Received: 31 August 2022 | Revised: 17 November 2022 | Accepted: 26 November 2022

DOI: 10.1111/cas.15682

REVIEW ARTICLE

Cancer Science WILEY

Bone morphogenetic protein signaling is a possible therapeutic target in gynecologic cancer

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Abstract

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor β (TGFβ) superfamily. BMPs play crucial roles in embryogenesis and bone remodeling. Recently, BMP signaling has been found to have diverse effects on different types of tumors. In this review, we summarized the effects of BMP signaling on gynecologic cancer. BMP signaling has tumor-promoting effects on ovarian cancer (OC) and endometrial cancer (EC), whereas it has tumor-suppressing effects on uterine cervical cancer (UCC). Interestingly, EC has frequent gain-of-function mutations in *ACVR1*, encoding one of the type I BMP receptors, which are also observed in fibrodysplasia ossificans progressiva and diffuse intrinsic pontine glioma. Little is known about the relationship between BMP signaling and other gynecologic cancers. Tumor-promoting effects of BMP signaling in OC and EC are dependent on the promotion of cancer stemness and epithelial–mesenchymal transition (EMT). In accordance, BMP receptor kinase inhibitors suppress the cell growth and migration of OC and EC. Since both cancer stemness and EMT are associated with chemoresistance, BMP signaling activation might also be an important mechanism by which OC and EC patients acquire chemoresistance. Therefore, BMP inhibitors are promising for OC and EC patients even if they become resistant to standard chemotherapy. In contrast, BMP signaling inhibits UCC growth in vitro. However, the in vivo effects of BMP signaling have not been elucidated in UCC. In conclusion, BMP signaling has a variety of functions, depending on the types of gynecologic cancer. Therefore, targeting BMP signaling should improve the treatment of patients with gynecologic cancer.

KEYWORDS
bone morphogenetic protein, cancer stem cell, chemoresistance, epithelial–mesenchymal transition, gynecologic cancer

Abbreviations: BMP, bone morphogenetic protein; EC, endometrial cancer; EMT, epithelial–mesenchymal transition; FN14, fibroblast growth factor-inducible 14; OC, ovarian cancer; TGFβ, transforming growth factor β; UCC, uterine cervical cancer.

Eri Suzuki and Risa Fukuda contributed equally to this work.

1 | INTRODUCTION

Bone morphogenetic proteins belong to the TGFβ superfamily (Figure 1A). BMPs perform crucial roles in organogenesis.[1] BMP ligands bind to type I and type II cell surface kinase-associated receptors.[1] Each BMP ligand has a different binding affinity to these two receptors (Figure 1B). BMP antagonists such as Noggin and Gremlin block ligand binding[2] (Figure 1C). The coordination of BMPs and antagonists is important for embryonic development and disease progression.[2] For instance, concentration gradients of BMP4 and Noggin define the dorsoventral patterning of vertebrate embryos.[3] A Gremlin–BMP axis modulates renal fibrosis in humans.[4] Type I receptors consist of ACVRL1, ACVR1, BMPR1A, and BMPR1B, whereas type II receptors consist of ACVR2A, ACVR2B and BMPR2 (Figure 1B). Upon ligand binding, type II receptors phosphorylate and activate type I receptors to induce SMAD1/5 phosphorylation, as well as the activation of non-SMAD signaling pathways, including phosphatidylinositol-3′-kinase (PI3K)/AKT and MAP kinase pathways (Figure 2). Phosphorylated SMAD1/5 translocate to the nucleus and activate transcription after forming complexes with SMAD4 (Figure 2). The ID family genes are well known downstream targets.[5–7] SNAIL and SLUG, EMT transcription factors, are also induced after BMP stimulation in OC and EC cells.[8,9]

Endothelial cell differentiation, as well as arterial/venous and lymphatic specification, require BMPs.[10] As ACVRL1 is mainly expressed on endothelial cells among type I receptors, BMP9 and BMP10 with high affinity to ACVRL1 play pivotal roles in angiogenesis.[11] Accordingly, the loss-of-function *ACVRL1* mutation causes hereditary hemorrhagic telangiectasia (HHT).[10] A loss-of-function mutation of *GDF2* encoding BMP9 is also the cause of HHT.[10] Furthermore, a *BMPR2* loss-of-function mutation causes pulmonary arterial hypertension (PAH).[10] Because both BMP9 supplementation and blockade improve PAH in a rodent model,[11] the relationship between BMP signaling and PAH remains to be elucidated. Several angiogenesis inhibitors, impinging on the vascular endothelial growth factor (VEGF) pathway, have been used to treat cancer patients.[12] However, they have shown limited survival benefits. Dalantercept, an ACVRL1-Fc fusion protein that blocks BMP signaling, has been developed as a novel angiogenesis inhibitor. Unfortunately, dalantercept has also displayed limited efficacy in several types of cancer, including endometrial and ovarian cancer[13] (Table 1).

Gynecologic cancer, which includes ovarian, endometrial, uterine cervical, vaginal, and vulvar cancer, has increasing importance because it threatens fertility. The ovary, fallopian tube, uterus, and the upper third of the vagina originate from Müllerian ducts. In contrast, Müllerian ducts regress in male fetuses due to apoptosis induction by anti-Müllerian hormone (AMH), which also belongs to the TGFβ superfamily and shares type I receptors with BMPs.[14] Loss-of-function mutations of *AMH* and *AMHR2* encoding type II receptor cause persistent Müllerian duct syndrome (PMDS).[14] PMDS patients retain both male and female reproductive organs, from which malignant degeneration occurs. As gynecologic cancer arises from Müllerian duct-derived

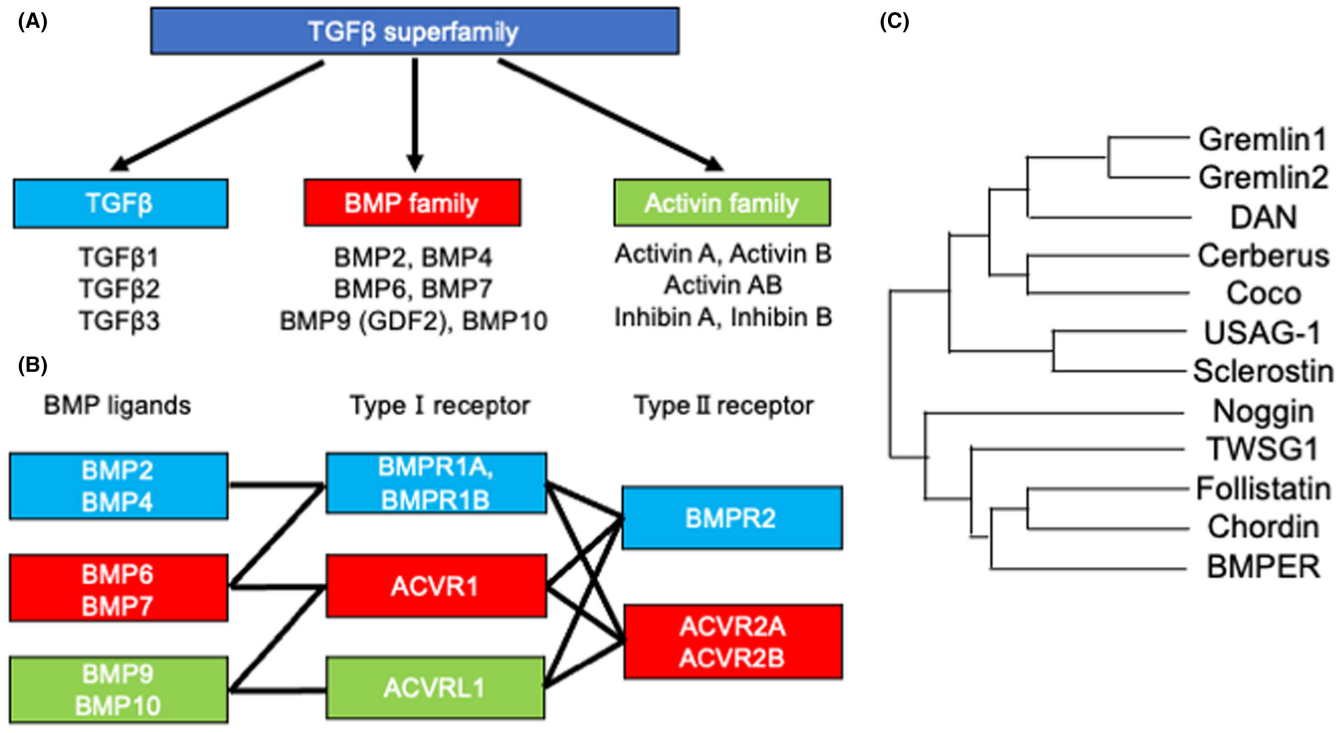

FIGURE 1 BMPs belong to the TGFβ superfamily. (A) The TGFβ superfamily is mainly divided into three subfamilies including TGFβ, BMP, and the Activin family. Other TGFβ family proteins also exist such as Nodal and anti-Müllerian hormone (AMH). (B) BMP ligands, classified into three groups, have different binding affinities for type I and type II receptors. (C) BMP antagonists are shown based on sequence similarity.

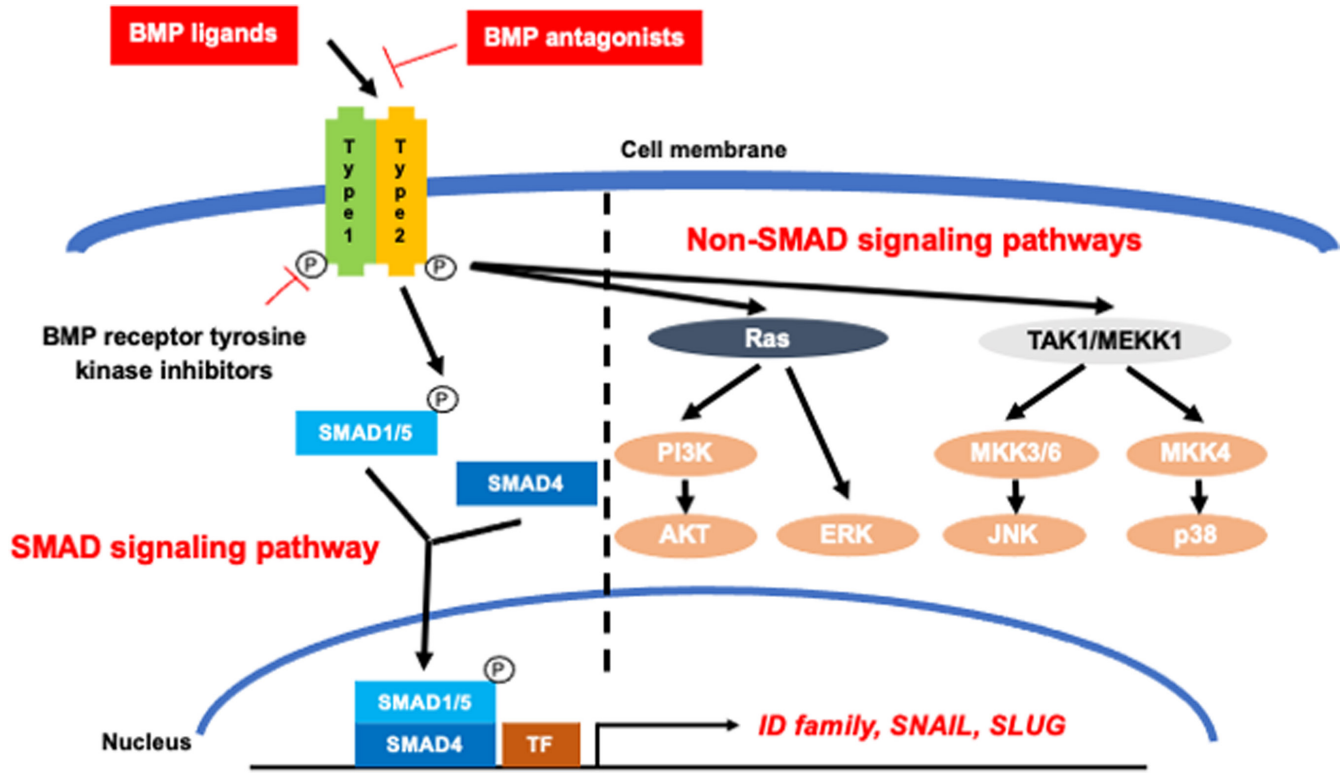

FIGURE 2 Overview of BMP signaling. Upon ligand binding, type II receptors phosphorylate and activate type I receptors to induce SMAD1/5 phosphorylation, as well as in the activation of certain non-SMAD signaling pathways. Phosphorylated SMAD1/5 translocate to the nucleus and activate transcription after forming complexes with SMAD4. TF, transcription factor.

organs, AMH has been anticipated to function as a tumor suppressor. Consistently, several studies have shown that AMH suppresses the proliferation of ovarian, endometrial, and uterine cervical cancers.[15–17] Conversely, recent reports have shown that AMH promotes gynecologic cancer cell growth and migration,[18] and several anti-AMHR2 antibodies have been demonstrated to exert tumor suppressive function on OC.[19,20] As BMPs share type I receptors with AMH,[1] BMP signaling may have an influence on gynecologic cancer.

In clinical settings, BMP ligands have been applied to patients, especially with orthotopic bone defects. Among BMP ligands, BMP2 is the most widely used. The Infuse™ bone graft (Medtronic, Dublin, Ireland), which contains recombinant human BMP2, is approved for anterior lumbar interbody fusion, acute tibial fractures, and maxillofacial reconstructions as an osteogenic device.[21–23] The OSTEOGROW, another osteogenic device, is based on recombinant human BMP6.[24] Clinical trials are underway for this device.[24] Conversely, BMP inhibitors have also been developed for diseases with BMP signaling activation, including fibrodysplasia ossificans progressiva (FOP) and diffuse intrinsic pontine glioma (DIPG) with a gain-of-function *ACVR1* mutation.[25] Several studies have shown the efficacy of ACVR1 inhibitors in preclinical models of FOP and DIPG.[26–28] Like ACVR1 inhibitors, most of the BMP inhibitors are BMP type I receptor kinase inhibitors.[25]

In this review, we focus on BMP signaling in gynecologic cancer. This knowledge will help developing a new molecular-targeted therapy for gynecologic cancer patients.

2 | BMP SIGNALING AND GYNECOLOGIC CANCER

2.1 | BMP signaling and ovarian cancer

Among gynecologic cancers, the relationship between BMP signaling and OC has been best studied. OC is the most lethal gynecologic cancer as it disseminates via EMT.[29] High-grade serous carcinoma (HGSC) is the most common subtype, accounting for 70% of OC. Although HGSC is highly sensitive to chemotherapy, it frequently relapses. The mechanism of recurrence is unclear, but the involvement of cancer stem cells has been suggested.[30] The Cancer Genome Atlas (TCGA) dataset analyses revealed that mRNA expression for most BMP ligands and receptors increased and that high *BMPR2* and *BMP7* mRNA expression levels correlated with poor survival in OC patients.[8,31] BMP2 expression was detected by immunohistochemistry, especially in HGSC with psammoma bodies.[32] Both BMP2 and BMP9 proteins were more abundantly expressed in OC than in normal ovarian surface epithelium.[33,34] High BMP2 protein expression was associated with poor survival in OC patients.[35] Furthermore, secretion of BMP4, as well as BMP2 from OC cells was detected, suggesting that BMP signaling is intact in OC.[5,8] In accordance, SMAD5 phosphorylation was confirmed by immunohistochemical staining and correlated with poor prognosis,[36] indicating the tumor-promoting role

TABLE 1 Effects of BMP inhibitors on gynecologic cancer

Drug	Mechanism	Cancer types	In vitro effects	In vivo effects	Clinical trials	Reference
Dalantercept	ACVRL1-Fc fusion protein	Endometrial cancer			Phase II (no OR)	13
		Ovarian cancer			Phase II (no OR)	13
Dorsomorphin	BMP receptor tyrosine kinase inhibitor	Ovarian cancer	Cell proliferation↓, cell migration↓, autophagy↑	Survival↑		36,55
DMH1	BMP receptor tyrosine kinase inhibitor	Ovarian cancer	Cell proliferation↓, sensitivity to cisplatin↑			31
LDN193189	BMP receptor tyrosine kinase inhibitor	Endometrial cancer	Cell proliferation↓, cell migration↓			9
		Ovarian cancer	Cell proliferation↓, cell migration↓, cell invasion↓	Survival→		8,55
RK783	BMP receptor tyrosine kinase inhibitor	Ovarian cancer	Cell proliferation↓	Tumor growth↓		8

Abbreviation: OR, objective response.

of BMP signaling. In addition, the secretion of BMP2 and BMP4 has been found in carcinoma-associated mesenchymal stem cells (CA-MSCs) as well as OC cells.[37] A positive feedback loop was identified between CA-MSC-derived BMP4 and OC-secreted Hedgehog (Figure 3A).[38]

In mice, double knockout of SMAD1/5, BMP-specific SMADs, caused ovarian granulosa cell tumors.[39] PDGFA was produced by SMAD1/5 double knockout granulosa cells by antagonizing with Sp1 on its promoter.[40] Therefore, not only suppression of BMP signaling but also the activation of PDGF signaling may be involved in the development of ovarian granulosa cell tumors. BMPR1A/1B double knockout mice also developed ovarian granulosa cell tumors, suggesting the tumor-suppressing function of BMP signaling in these tumors.[41] However, BMP signaling has been reported to have tumor-promoting roles in other OCs. Although BMP2 was initially reported to inhibit the colony formation of OC cells,[42] recent studies have shown that it promotes OC cell growth.[8,36] This discrepancy may be attributed to its concentration. BMP2 suppressed OC colony formation at 1000 ng/ml, a supraphysiological concentration.[42] Using high concentrations of recombinant growth factor preparations carries the risk that the observed effects are due to contamination in preparation of another potent growth factor. Such contamination has been observed, e.g., in preparation of GDF15.[43] In contrast, 20 ng/ml of BMP2 enhanced OC proliferation.[8] BMP2 was indispensable for OC organoid culture and Noggin, a BMP antagonist, attenuated initial organoid formation[44] (Table 2). Similarly, autocrine BMP9 promoted OC proliferation in an ACVR1-dependent manner.[34,45] Notch1 signaling activation was also involved in BMP9-stimulated OC growth.[45] We have identified that BMP2-induced OC proliferation was attributed to c-KIT induction.[8,46] Since c-KIT is a well known OC-associated stem cell marker,[47] BMP signaling could enhance OC stemness. Accordingly, BMP2 promoted OC sphere formation.[8] Interestingly, RNA sequencing revealed that BMP2 induction of c-KIT was partially triggered by FN14, a tumor necrosis factor (TNF) receptor superfamily[46] (Figure 3A). FN14 has been shown to increase in OC and to promote OC cell migration and invasion.[48,49] Therefore, a combination of BMP/c-KIT/FN14 signaling blockade might be efficient for the treatment of OC patients.

BMP signaling drives EMT in OC. Both BMP2/4 induced SNAIL and SLUG, EMT transcription factors, in OC cells.[8,35,50] Accordingly, E-cadherin expression was suppressed by BMP2/4 stimulation, leading to EMT-like morphological changes.[8,50] Consequently, both ligands enhanced OC cell migration and invasion[8,50] (Figure 3A). Chordin, a BMP antagonist with decreased expression in OC, conversely, inhibited migration and invasion[51] (Table 2). Indeed, high BMP2 expression correlated with lymph node metastasis,[52] suggesting that BMP signaling triggers OC metastasis through EMT induction. We have proved that BMP2-enhanced migration and invasion were dependent on SLUG induction.[8] Furthermore, SLUG induction was FN14 dependent, as was c-KIT[46] (Figure 3A). Consistently, FN14 knockdown inhibited BMP2-induced cell migration.[46] Considering that FN14 is a downstream effector of BMP signaling, dual BMP/FN14 signaling inhibition might efficiently suppress OC metastasis.

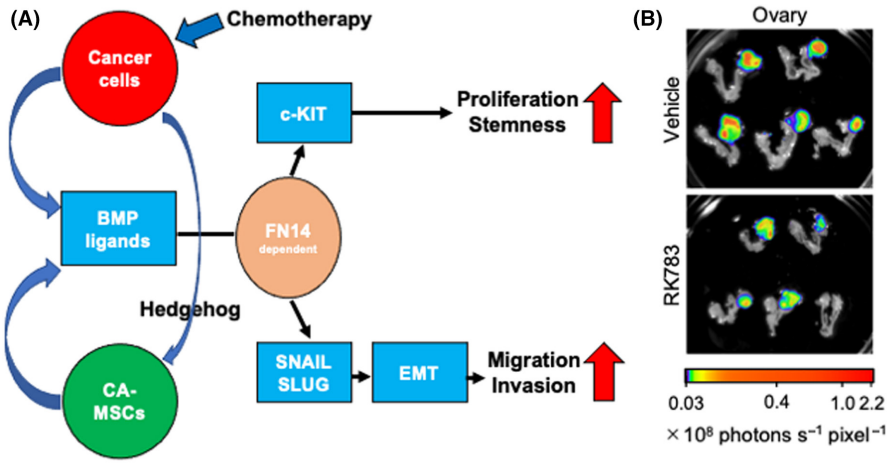

FIGURE 3 Model of BMP signaling in ovarian and endometrial cancer. (A) BMP secretion from cancer cells and carcinoma-associated mesenchymal stem cells (CA-MSCs) is triggered by chemotherapy and cancer-secreted Hedgehog, respectively. Secreted BMPs enhance cancer proliferation and stemness via c-KIT induction. BMPs also trigger EMT through SNAIL/SLUG induction, leading to the enhancement of migration and invasion. These effects are partially attributed to FN14 induction. (B) RK783, a newly developed BMP receptor kinase inhibitor, suppressed SKOV3 OC cell growth in orthotopic xenografted mice; adapted from Fukuda et al.[8]

TABLE 2 Effects of BMP antagonists on gynecologic cancer

Antagonist	Cancer types	In vitro effects	In vivo effects	Reference
Noggin	Ovarian cancer	Organoid formation↓		44
Chordin	Ovarian cancer	Cell migration↓, cell invasion↓		51
Gremlin2	Endometrial cancer	Cell proliferation↓		61
TWSG1	Endometrial cancer	Sphere formation↓, cell migration↓		9
BMPER	Cervical cancer		Unknown (expressed in tissues)	69
Gremlin1	Cervical cancer	Sphere formation↑	Correlation with worse survival and larger tumor volume	70

As an FN14 blocking antibody has been developed,[53] it may act effectively for OC patients with activated BMP signaling.

At present, a combination of platinum-based carboplatin and paclitaxel is a first-line chemotherapeutic regimen for OC. Once patients become resistant to platinum-based chemotherapy, only limited treatment options remain. As the promotion of cancer stem cells and EMT are related to resistance, novel agents limiting the numbers of cancer stem cells and the potency of EMT may be useful.[29,30] As previously described, BMP signaling modulates both stemness and EMT of OC.[8] Thus, BMP signaling activation might lead to chemoresistance. Accordingly, carboplatin, a key chemotherapeutic agent, enhanced BMP2 secretion from OC cells.[8] Similarly, another platinum-based cisplatin increased BMP4 mRNA expression in OC cells.[54] Although the mechanism of chemotherapy-induced BMP secretion is unknown, these results suggest that BMP signaling inhibition might reverse chemoresistance. To date, several BMP inhibitors, including dorsomorphin, DMH1, and LDN193189 have been developed.[25] These compounds suppress BMP signaling through kinase inhibition of type I receptors.[25] The efficacy of BMP inhibitors has been shown in OC[31,36,55] (Table 1). As previously described, dalantercept, an ACVRL1-Fc fusion protein, demonstrated limited efficacy in OC patients.[13] This might be due to lower ACVRL1 expression in OC. In contrast, dorsomorphin efficiently attenuated OC cell proliferation and migration, leading to prolonged survival of xenografted mice.[36,55] DMH1 also inhibited OC cell proliferation in vitro.[31] Although LDN193189 inhibited OC cell proliferation and migration as well,[8] it had no effect on xenografted mouse survival.[55] We recently demonstrated that RK783, a newly developed BMP receptor kinase inhibitor, suppressed SMAD1/5 phosphorylation and OC cell growth in orthotopic xenografted mice[8] (Table 1; Figure 3B). Moreover, DMH1 enhanced the sensitivity to cisplatin and regulated gene expression involved in platinum resistance in OC[31] (Table 1). Thus, BMP inhibitors are promising for OC, regardless of sensitivity to standard chemotherapy.

2.2 | BMP signaling and endometrial cancer

The significance of BMP signaling in uterine receptivity has been recently shown.[56,57] As BMP signaling modulates uterine decidualization, uterine endometrium-specific deletion of BMP-related genes leads to infertility via implantation failure in mice.[56,57] However, endometrial carcinogenesis has not been evaluated. As EC develops from infertile endometrium, BMPs may exert important roles

in endometrial carcinogenesis. Both endometrial stromal cells and vascular endothelial cells of the uterine corpus retained BMP2.[58,59] Therefore, BMP2 is able to stimulate EC. Different from BMP2, BMP7 is present in both endometrial epithelium and stroma.[58] Interestingly, BMP2 secretion from endometrial stromal cells was attenuated in women with uterine leiomyoma.[60] We have reported the tumor-promoting effects of BMP2 in EC.[9,46] BMP2 promoted sphere formation and cell migration of Ishikawa EC cells through the same mechanism as in OC[9,46] (Figure 3A). BMP2 enhanced sphere formation through c-KIT induction, whereas it provoked migration via SLUG-dependent EMT induction.[9] These effects were canceled by FN14 knockdown.[46] In contrast, Gremlin 2, a BMP antagonist, inhibited EC cell growth[61] (Table 2). Reports also showed that TWSG1, another BMP antagonist, reversed EC sphere formation and migration by antagonizing BMP7[9] (Table 2). Furthermore, DNA hypomethylation of *BMP4* and *BMP7* genes was associated with poor survival in EC patients.[62] These results indicated that BMP signaling inhibition is promising for the treatment of EC patients as well as OC patients.

2.3 | BMP signaling and uterine cervical cancer

Uterine cervical cancer is caused by human papillomavirus (HPV) infection.[63] Furthermore, HPV vaccines effectively prevent uterine cervical carcinogenesis worldwide.[63] Nevertheless, the mechanisms of UCC progression are not fully understood. TGFβ has been reported to attenuate UCC growth.[64,65] Similarly, BMP7 inhibited UCC growth by causing telomere shortening through hTERT inhibition.[66] BMP4 suppressed UCC growth via a different mechanism than BMP2.[67] BMP4 inhibited tumor angiogenesis via VEGF attenuation in a thrombospondin-1-dependent manner.[67] Although the expression of BMPs has not been elucidated, the expression of several BMP antagonists has been shown in UCC.[68–70] BMPER, a BMP antagonist, is expressed in UCC at both the protein and mRNA levels[69] (Table 2). However, the function of BMPER has not been shown. Gremlin 1, another BMP antagonist, is also expressed in UCC[68,70] (Table 2). High Gremlin 1 mRNA expression is correlated with poor survival and larger tumor volume, indicating the tumor-promoting functions of Gremlin 1.[70] Accordingly, exogenous Gremlin 1 enhanced sphere formation and the proportion of side population cells in CaSki cells, indicating that Gremlin 1 promotes cancer stemness.[70] These effects were partially attributed to Nanog induction.[70] These results suggest that BMP signaling might suppress UCC, unlike OC and EC.

2.4 | BMP signaling and other gynecologic cancer

Diethylstilbestrol exposure in utero triggers vaginal adenosis, from which clear cell adenocarcinoma can arise.[71] As BMP4 coordinates with fibroblast growth factor and Activin A to define vaginal cell fate, disruption of BMP4 signaling plays an important role in diethylstilbestrol-triggered vaginal carcinogenesis.[72] Considering that BMP4 is also important for external genitalia formation,[73] BMP4 might inhibit vulvar cancer as well as vaginal cancer. Further studies are needed to clarify the importance of BMP signaling in these cancers.

3 | CONCLUSION

BMP signaling has tumor-promoting effects on OC and EC, whereas it has tumor-suppressing effects on UCC. Little is known about the relationship between BMP signaling and other gynecologic cancers.

The tumor-promoting effects of BMP signaling in OC/EC are dependent on the promotion of stemness and EMT. As both stemness and EMT are associated with chemoresistance, BMP signaling activation might be an important mechanism by which OC/EC patients acquire chemoresistance. Therefore, BMP inhibitors are promising for OC/EC patients even if they become resistant to standard chemotherapy.

In contrast, BMP signaling inhibits UCC growth. Because UCC causes osteolytic bone metastasis, osteogenic devices such as the Infuse™ bone graft and OSTEOGROW may be useful for patients with bone metastatic UCC.

In conclusion, BMP signaling has a variety of effects on different types of gynecologic cancer. Targeting BMP signaling should improve the treatment of gynecologic cancer patients. Clinical trials targeting BMP signaling in gynecologic cancer patients are desperately needed.

AUTHOR CONTRIBUTIONS

TF: Conceptualization, Writing – Original draft; review and editing. ES: Writing – Original draft. RF: Writing – Original draft.

ACKNOWLEDGMENTS

We thank Agapiti Chuwa (University of Dar es Salaam, Tanzania) for English language editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

All animal studies were approved by the Animal Experiment Committee of the Graduate School of Medicine, The University of Tokyo (Medicine-P16-140).

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REFERENCES

1. Miyazono K, Kamiya Y, Morikawa M. Bone morphogenetic protein receptors and signal transduction. *J Biochem*. 2010;147:35-51.
2. Correns A, Zimmermann LA, Baldock C, Sengle G. BMP antagonists in tissue development and disease. *Matrix Biol Plus*. 2021;11:100071.

3. Sasai Y, De Robertis EM. Ectodermal patterning in vertebrate embryos. *Dev Biol*. 1997;182:5-20.
4. Roxburgh SA, Murphy M, Pollock CA, Brazil DP. Recapitulation of embryological programmes in renal fibrosis--the importance of epithelial cell plasticity and developmental genes. *Nephron Physiol*. 2006;103:139-148.
5. Shepherd TG, Nachtigal MW. Identification of a putative autocrine bone morphogenetic protein-signaling pathway in human ovarian surface epithelium and ovarian cancer cells. *Endocrinology*. 2003;144:3306-3314.
6. Shepherd TG, Thériault BL, Nachtigal MW. Autocrine BMP4 signalling regulates ID3 proto-oncogene expression in human ovarian cancer cells. *Gene*. 2008;414:95-105.
7. Ho CC, Zhou X, Mishina Y, Bernard DJ. Mechanisms of bone morphogenetic protein 2 (BMP2) stimulated inhibitor of DNA binding 3 (Id3) transcription. *Mol Cell Endocrinol*. 2011;332:242-252.
8. Fukuda T, Fukuda R, Tanabe R, et al. BMP signaling is a therapeutic target in ovarian cancer. *Cell Death Discov*. 2020;6:139.
9. Fukuda T, Fukuda R, Miyazono K, Heldin CH. Tumor promoting effect of BMP signaling in endometrial cancer. *Int J Mol Sci*. 2021;22:7882.
10. Goumans MJ, Zwijsen A, Ten Dijke P, Bailly S. Bone morphogenetic proteins in vascular homeostasis and disease. *Cold Spring Harb Perspect Biol*. 2018;10:a031989.
11. Desroches-Castan A, Tillet E, Bouvard C, Bailly S. BMP9 and BMP10: two close vascular quiescence partners that stand out. *Dev Dyn*. 2022;251:178-197.
12. Grothey A, Galanis E. Targeting angiogenesis: progress with anti-VEGF treatment with large molecules. *Nat Rev Clin Oncol*. 2009;6:507-518.
13. de Vinuesa AG, Bocci M, Pietras K, Ten Dijke P. Targeting tumour vasculature by inhibiting activin receptor-like kinase (ALK)1 function. *Biochem Soc Trans*. 2016;44:1142-1149.
14. di Clemente N, Racine C, Pierre A, Taieb J. Anti-Müllerian hormone in female reproduction. *Endocr Rev*. 2021;42:753-782.
15. Donahoe PK, Fuller AF Jr, Scully RE, Guy SR, Budzik GP. Mullerian inhibiting substance inhibits growth of a human ovarian cancer in nude mice. *Ann Surg*. 1981;194:472-480.
16. Renaud EJ, MacLaughlin DT, Oliva E, Rueda BR, Donahoe PK. Endometrial cancer is a receptor-mediated target for Mullerian inhibiting substance. *Proc Natl Acad Sci USA*. 2005;102:111-116.
17. Barbie TU, Barbie DA, MacLaughlin DT, Maheswaran S, Donahoe PK. Mullerian inhibiting substance inhibits cervical cancer cell growth via a pathway involving p130 and p107. *Proc Natl Acad Sci USA*. 2003;100:15601-15606.
18. Chauvin M, Garambois V, Colombo PE, et al. Anti-Müllerian hormone (AMH) autocrine signaling promotes survival and proliferation of ovarian cancer cells. *Sci Rep*. 2021;11:2231.
19. Prat M, Salon M, Allain T, et al. Murlentamab, a low Fucosylated anti-Müllerian hormone type II receptor (AMHRII) antibody, exhibits anti-tumor activity through tumor-associated macrophage Reprogrammation and T cell activation. *Cancers (Basel)*. 2021;13:1845.
20. Chauvin M, Garambois V, Choblet S, et al. Anti-Müllerian hormone concentration regulates activin receptor-like kinase-2/3 expression levels with opposing effects on ovarian cancer cell survival. *Int J Oncol*. 2021;59:43.
21. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine*. 2002;27:2396-2408.
22. Baskin DS, Ryan P, Sonntag V, Westmark R, Widmayer MA. A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. *Spine*. 2003;28:1219-1224; discussion 1225.
23. Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Puno RM, Johnson JR. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. *Spine*. 2005;30:1694-1698.
24. Vukicevic S, Oppermann H, Verbanac D, et al. The clinical use of bone morphogenetic proteins revisited: a novel biocompatible carrier device OSTEOGROW for bone healing. *Int Orthop*. 2014;38:635-647.
25. Rooney L, Jones C. Recent advances in ALK2 inhibitors. *ACS Omega*. 2021;6:20729-20734.
26. Yu PB, Deng DY, Lai CS, et al. BMP type I receptor inhibition reduces heterotopic [corrected] ossification. *Nat Med*. 2008;14:1363-1369.
27. Han HJ, Jain P, Resnick AC. Shared ACVR1 mutations in FOP and DIPG: opportunities and challenges in extending biological and clinical implications across rare diseases. *Bone*. 2018;109:91-100.
28. Carvalho D, Taylor KR, Olaciregui NG, et al. ALK2 inhibitors display beneficial effects in preclinical models of ACVR1 mutant diffuse intrinsic pontine glioma. *Commun Biol*. 2019;2:156.
29. Kumari A, Shonibare Z, Monavarian M, et al. TGFβ signaling networks in ovarian cancer progression and plasticity. *Clin Exp Metastasis*. 2021;38:139-161.
30. Mihanfar A, Aghazadeh Attari J, Mohebbi I, et al. Ovarian cancer stem cell: a potential therapeutic target for overcoming multidrug resistance. *J Cell Physiol*. 2019;234:3238-3253.
31. Hover LD, Young CD, Bhola NE, et al. Small molecule inhibitor of the bone morphogenetic protein pathway DMH1 reduces ovarian cancer cell growth. *Cancer Lett*. 2015;368:79-87.
32. Kiyozuka Y, Nakagawa H, Senzaki H, et al. Bone morphogenetic protein-2 and type IV collagen expression in psammoma body forming ovarian cancer. *Anticancer Res*. 2001;21:1723-1730.
33. Le Page C, Ouellet V, Madore J, et al. Gene expression profiling of primary cultures of ovarian epithelial cells identifies novel molecular classifiers of ovarian cancer. *Br J Cancer*. 2006;94:436-445.
34. Herrera B, van Dinther M, Ten Dijke P, Inman GJ. Autocrine bone morphogenetic protein-9 signals through activin receptor-like kinase-2/Smad1/Smad4 to promote ovarian cancer cell proliferation. *Cancer Res*. 2009;69:9254-9262.
35. Le Page C, Puiffe ML, Meunier L, et al. BMP-2 signaling in ovarian cancer and its association with poor prognosis. *J Ovarian Res*. 2009;2:4.
36. Peng J, Yoshioka Y, Mandai M, et al. The BMP signaling pathway leads to enhanced proliferation in serous ovarian cancer – a potential therapeutic target. *Mol Carcinog*. 2016;55:335-345.
37. McLean K, Gong Y, Choi Y, et al. Human ovarian carcinoma–associated mesenchymal stem cells regulate cancer stem cells and tumorigenesis via altered BMP production. *J Clin Invest*. 2011;121:3206-3219.
38. Coffman LG, Choi YJ, McLean K, Allen BL, di Magliano MP, Buckanovich RJ. Human carcinoma-associated mesenchymal stem cells promote ovarian cancer chemotherapy resistance via a BMP4/HH signaling loop. *Oncotarget*. 2016;7:6916-6932.
39. Pangas SA, Li X, Umans L, et al. Conditional deletion of Smad1 and Smad5 in somatic cells of male and female gonads leads to metastatic tumor development in mice. *Mol Cell Biol*. 2008;28:248-257.
40. Tripurani SK, Cook RW, Eldin KW, Pangas SA. BMP-specific SMADs function as novel repressors of PDGFA and modulate its expression in ovarian granulosa cells and tumors. *Oncogene*. 2013;32:3877-3885.
41. Edson MA, Nalam RL, Clementi C, et al. Granulosa cell-expressed BMPR1A and BMPR1B have unique functions in regulating fertility but act redundantly to suppress ovarian tumor development. *Mol Endocrinol*. 2010;24:1251-1266.

42. Soda H, Raymond E, Sharma S, et al. Antiproliferative effects of recombinant human bone morphogenetic protein-2 on human tumor colony-forming units. *Anticancer Drugs*. 1998;9:327-331.
43. Olsen OE, Skjærvik A, Størdal BF, Sundan A, Holien T. TGF-β contamination of purified recombinant GDF15. *PLoS One*. 2017;12:e0187349.
44. Hoffmann K, Berger H, Kulbe H, et al. Stable expansion of high-grade serous ovarian cancer organoids requires a low-Wnt environment. *EMBO J*. 2020;39:e104013.
45. Yang L, Bai Y, Zhang C, et al. Overexpression of BMP9 promotes ovarian cancer progression via Notch1 signaling. *Neoplasma*. 2021;68:1190-1200.
46. Fukuda T, Fukuda R, Koinuma D, Moustakas A, Miyazono K, Heldin CH. BMP2-induction of FN14 promotes protumorigenic signaling in gynecologic cancer cells. *Cell Signal*. 2021;87:110146.
47. Mazzoldi EL, Pavan S, Pilotto G, et al. A juxtacrine/paracrine loop between C-kit and stem cell factor promotes cancer stem cell survival in epithelial ovarian cancer. *Cell Death Dis*. 2019;10:412.
48. Gu L, Dai L, Cao C, et al. Functional expression of TWEAK and the receptor Fn14 in human malignant ovarian tumors: possible implication for ovarian tumor intervention. *PLoS One*. 2013;8:e57436.
49. Dai L, Gu L, Ding C, Qiu L, Di W. TWEAK promotes ovarian cancer cell metastasis via NF-kappaB pathway activation and VEGF expression. *Cancer Lett*. 2009;283:159-167.
50. Thériault BL, Shepherd TG, Mujoomdar ML, Nachtigal MW. BMP4 induces EMT and rho GTPase activation in human ovarian cancer cells. *Carcinogenesis*. 2007;28:1153-1162.
51. Moll F, Millet C, Noël D, et al. Chordin is underexpressed in ovarian tumors and reduces tumor cell motility. *FASEB J*. 2006;20:240-250.
52. Zırh EB, Kapaklı ET, Dolgun A, Usubütün A, Zeybek ND. The expression of BMP, integrin, ZEB2 in ovarian high-grade serous carcinoma in relation with lymph node metastasis. *Growth Factors*. 2022;40:153-162.
53. Zhou H, Marks JW, Hittelman WN, et al. Development and characterization of a potent immunoconjugate targeting the Fn14 receptor on solid tumor cells. *Mol Cancer Ther*. 2011;10:1276-1288.
54. Laatio L, Myllynen P, Serpi R, et al. BMP-4 expression has prognostic significance in advanced serous ovarian carcinoma and is affected by cisplatin in OVCAR-3 cells. *Tumour Biol*. 2011;32:985-995.
55. Ali JL, Lagasse BJ, Minuk AJ, et al. Differential cellular responses induced by dorsomorphin and LDN-193189 in chemotherapy-sensitive and chemotherapy-resistant human epithelial ovarian cancer cells. *Int J Cancer*. 2015;136:E455-E469.
56. Monsivais D, Clementi C, Peng J, et al. BMP7 induces uterine receptivity and blastocyst attachment. *Endocrinology*. 2017;158:979-992.
57. Monsivais D, Nagashima T, Prunskaite-Hyyryläinen R, et al. Endometrial receptivity and implantation require uterine BMP signaling through an ACVR2A-SMAD1/SMAD5 axis. *Nat Commun*. 2021;12:3386.
58. Erickson GF, Fuqua L, Shimasaki S. Analysis of spatial and temporal expression patterns of bone morphogenetic protein family members in the rat uterus over the estrous cycle. *J Endocrinol*. 2004;182:203-217.
59. Fadare O, Renshaw IL, Liang SX. Patterns of bone morphogenetic protein-2 expression in smooth muscle tumors of the uterine corpus and other uterine tissues. *Appl Immunohistochem Mol Morphol*. 2011;19:352-359.
60. Sinclair DC, Mastroyannis A, Taylor HS. Leiomyoma simultaneously impair endometrial BMP-2-mediated decidualization and anticoagulant expression through secretion of TGF-β3. *J Clin Endocrinol Metab*. 2011;96:412-421.
61. Tsubamoto H, Sakata K, Sakane R, et al. Gremlin 2 is repressed in invasive endometrial cancer and inhibits cell growth In vitro. *Anticancer Res*. 2016;36:199-203.
62. Hsu YT, Gu F, Huang YW, et al. Promoter hypomethylation of EpCAM-regulated bone morphogenetic protein gene family in recurrent endometrial cancer. *Clin Cancer Res*. 2013;19:6272-6285.
63. Gaffney DK, Hashibe M, Kepka D, Maurer KA, Werner TL. Too many women are dying from cervix cancer: problems and solutions. *Gynecol Oncol*. 2018;151:547-554.
64. Kim JW, Kim HS, Kim IK, et al. Transforming growth factor-beta 1 induces apoptosis through down-regulation of c-myc gene and overexpression of p27Kip1 protein in cervical carcinoma. *Gynecol Oncol*. 1998;69:230-236.
65. Choi HH, Jong HS, Hyun Song S, You Kim T, Kyeong Kim N, Bang YJ. p130 mediates TGF-beta-induced cell-cycle arrest in Rb mutant HT-3 cells. *Gynecol Oncol*. 2002;86:184-189.
66. Cassar L, Li H, Pinto AR, Nicholls C, Bayne S, Liu JP. Bone morphogenetic protein-7 inhibits telomerase activity, telomere maintenance, and cervical tumor growth. *Cancer Res*. 2008;68:9157-9166.
67. Tsuchida R, Osawa T, Wang F, et al. BMP4/Thrombospondin-1 loop paracrinically inhibits tumor angiogenesis and suppresses the growth of solid tumors. *Oncogene*. 2014;33:3803-3811.
68. Namkoong H, Shin SM, Kim HK, et al. The bone morphogenetic protein antagonist gremlin 1 is overexpressed in human cancers and interacts with YWHAH protein. *BMC Cancer*. 2006;6:74.
69. Heinke J, Kerber M, Rahner S, et al. Bone morphogenetic protein modulator BMPER is highly expressed in malignant tumors and controls invasive cell behavior. *Oncogene*. 2012;31:2919-2930.
70. Sato M, Kawana K, Fujimoto A, et al. Clinical significance of Gremlin 1 in cervical cancer and its effects on cancer stem cell maintenance. *Oncol Rep*. 2016;35:391-397.
71. Laronda MM, Unno K, Butler LM, Kurita T. The development of cervical and vaginal adenosis as a result of diethylstilbestrol exposure in utero. *Differentiation*. 2012;84:252-260.
72. Terakawa J, Serna VA, Nair DM, et al. SIX1 cooperates with RUNX1 and SMAD4 in cell fate commitment of Müllerian duct epithelium. *Cell Death Differ*. 2020;27:3307-3320.
73. Suzuki K, Bachiller D, Chen YP, et al. Regulation of outgrowth and apoptosis for the terminal appendage: external genitalia development by concerted actions of BMP signaling [corrected]. *Development*. 2003;130:6209-6220.

How to cite this article: Fukuda T, Suzuki E, Fukuda R. Bone morphogenetic protein signaling is a possible therapeutic target in gynecologic cancer. *Cancer Sci*. 2023;114:722-729. doi:10.1111/cas.15682