LAJOMS

Review

January - March 2022
Vol. 2, no. 1 / pp. 19-24

Use of bone morphogenetic proteins in reconstruction of maxillofacial defects caused by oral squamous cell carcinoma: is their use safe?

Uso de proteínas morfogenéticas óseas en la reconstrucción de defectos maxilofaciales causados por carcinoma escamoso oral: ¿es seguro su uso?

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Keywords:
Bone morphogenetic proteins, oral squamous cell carcinoma, maxillomandibular reconstruction.

Palabras clave:
Proteínas morfogenéticas óseas, carcinoma oral de células escamosas, reconstrucción cráneo-maxilofacial.

ABSTRACT

In the maxillofacial region, large defects that require bone reconstruction most commonly arise from resection of oral squamous cell carcinoma advanced-stage. Human bone morphogenetic proteins (BMPs), have recently gained favor as a potential growth factor for *de novo* bone formation in maxillofacial reconstruction because of its osteoinductive activity, but its use for patients with craniomaxillofacial defects after oral squamous cell carcinoma resections remains contraindicated due to the paucity of data regarding the biologic effects of BMPs on cancer. The purpose of this study is to examines the role of BMPs in oral malignancy. Depending on the BMPs ligand and cancer type, BMPs can either promote or inhibit tumorigenesis. According to the data collected by us, we do not recommend the use of BMPs to reconstruct maxillofacial bone defects caused by resection of oral squamous cell carcinoma.

RESUMEN

En la región maxilofacial, los grandes defectos que requieren reconstrucciones óseas surgen con mayor frecuencia de la resección del carcinoma oral de células escamosas en estadios avanzados. Las proteínas morfogenéticas óseas humanas (BMP) recientemente han ganado popularidad como un factor de crecimiento potencial para la formación ósea de novo en la reconstrucción debido a su actividad osteoinductora; sin embargo, su uso en pacientes con defectos craneomaxilofaciales después de resecciones de carcinoma de células escamosas oral sigue estando contraindicado debido a la escasez de datos sobre los efectos biológicos de las BMP sobre el cáncer. El propósito de este estudio es examinar el papel de las BMP en la malignidad oral. Según el ligando de BMP y el tipo de cáncer, las BMP pueden promover o inhibir la tumorigénesis. Según los datos recopilados por esta investigación, no recomendamos el uso de BMP para reconstruir los defectos óseos maxilofaciales causados por la resección del carcinoma oral de células escamosas.

Introduction

Maxillofacial cancer, including lesions arising from the oral cavity, oropharynx and face, is one of the leading causes of cancer-related deaths worldwide.[1] More than 90% of head and neck cancers are oral squamous cell carcinoma (OSCC), which is associated with smoking, drinking alcohol and betel nut chewing.[2] In the maxillofacial region, large defects that require bone reconstruction most commonly arise from resection of advanced-stage OSCC. This critical-size osseous defects cannot heal without surgical intervention and pose a significant challenge to craniofacial reconstruction.[3,4] The gold standard for large defects is now vascularized free tissue flaps. This approach successfully restores form and function when performed by appropriately trained surgeons. However, free tissue transfer has limitations, including donor site morbidity, difficulty restoring the complex three-dimensional structure of the defect, and significantly extending the surgical time.[5]

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Received: 16/09/2021
Accepted: 15/10/2021

doi: 10.35366/103405

How to cite: Solano N, Parra E, Peraza A, Dueñes G. Use of bone morphogenetic proteins in reconstruction of maxillofacial defects caused by oral squamous cell carcinoma: is their use safe? Lat Am J Oral Maxillofac Surg. 2022; 2 (1): 19-24. https://dx.doi.org/10.35366/103405

These limitations have led to newer regenerative approaches using tissue engineering concepts being considered for the reconstruction of these defects. One such tissue engineering approach uses growth factors and scaffolds to support osteogenesis. In particular, recombinant human bone morphogenetic proteins (rhBMP), have recently gained favor as a potential growth factor for *de novo* bone formation in maxillofacial reconstruction because of its osteoinductive activity.[6]

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor TGF-β superfamily that mediates a multitude of developmental processes in various tissues. This family of more than 20 proteins has been shown to have roles in cellular lineage commitment, differentiation, proliferation, patterning/morphogenesis, cellular maintenance/survival, and apoptosis.[7,8] Preclinical animal models and clinical experience from orthopedics show that BMPs are critically important osteoinductive molecules for regenerative approaches.[9] Two recombinant human BMPs (rhBMP-2 and rhBMP-7) are now commercially available and have already led to improvements in the treatment of patients undergoing surgery for spinal fusion and long bone nonunions.[10,11] Human recombinant BMP-2 is also approved by the U.S. Food and Drug Administration (FDA) for some orodental applications, but its use for patients with craniomaxillofacial defects after OSCC resections remains contraindicated due to the paucity of data regarding the biologic effects of BMPs on cancer.[12]

The potential role of BMPs in malignant transformation and progression of cancer is poorly understood.[13] BMPs overexpression has been demonstrated to result in changes in cell morphology and increased cell motility and invasiveness in the pancreatic, gastric, prostate and breast cancer cells.[12-17] Bach et al.[18] analyzed the double role of BMPs in cancer, and they claimed 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. There are no unifying conclusions that can be made from the currently available data as to whether BMPs promotes, inhibits, or has no role in carcinogenesis of OSCC. Therefore, it is imperative to establish methods that could accurately evaluate whether BMPs exogenously grafted for maxillofacial hard tissue regeneration is associated with OSCC *(Figure 1)*.[18]

Commercially available rhBMP-2 is the only FDA approved product for intraoral applications in the craniofacial skeleton; however, off-label use of rhBMP-2 and rhBMP-7 has been attempted in some cases to solve other particularly significant reconstructive challenges in the craniomaxillofacial area.[19] Notable cases involve the reconstruction of the cranial vault, the reconstruction of alveolar cleft deformities, and the reconstruction of bone defects secondary to traumatic injury or neoplasms.[4,6] It is therefore important to deepen the study about the safety in the use of BMPs and the biological effects on malignant neoplasms before using this molecule for the reconstruction of maxillofacial bone defects in the vicinity of a resected tumor or in patients undergoing treatment for malignancy. From a practical standpoint, our knowledge in this area needs to be increased before considering the translation of basic science advances in bone tissue engineering using BMPs for reconstruction of craniomaxillofacial defects in patients treated for OSCC *(Figure 2)*. The purpose of this study is to examines the role of BMPs in oral malignancy.

Role of BMPS in oral squamous cell carcinoma

Many studies analyze the role of BMPs in cancer.[12-58] An ideal osseous grafting treatment should involve the use of a bone-inductive material that would be reliable, biocompatible, long lasting and capable of regenerate with minimal morbidity. Particulate marrow and cancellous autogenous bone meet these requirements, but they must be harvested from a donor site, which often results in insufficient bone graft material, added cost and patient harvest-graft-site discomfort. BMPs are a group of osteoinductive, sequentially arranged amino acids and polypeptides that are capable of stimulating adult mesenchymal stem cells to become osteoblastic and form bone.[48] Recombinant BMP-2 has been FDA approved for its use as an alternative to autografts in spinal fusions, adjuvant use in open tibia fractures, maxillary sinus augmentation and for alveolar ridge defects associated with extraction sockets in the form of bone graft coating, membranes, or solutions.[40,49]

Currently, recombinant human BMPs (rhBMP-2 and rhBMP-7) are the most extensively studied proteins and are commercially available for specific indications. The suggested human therapeutic doses (0.88 mg/mL of sterile water for rhBMP-7 and 1.50 mg/mL of sterile water for rhBMP-2) were

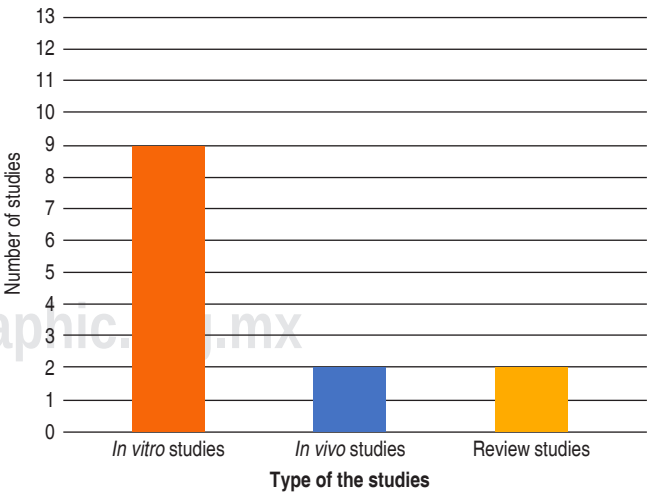

Figure 1: *Type and number of BMPs and oral squamous cell carcinoma (OSCC) studies in the literature.*

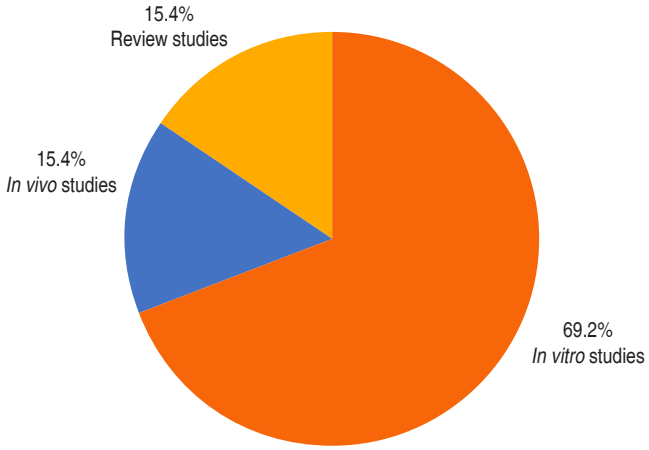

Figure 2: *Type of BMPs and oral squamous cell carcinoma (OSCC) studies in the literature.*

derived from nonhuman primate studies and verified in clinical orthopedic studies. The doses of rhBMP required to induce bone formation in humans must be higher than endogenous concentrations of BMPs. Because BMPs act locally, the proteins must be transferred to the implantation site via a carrier matrix, which prevents prompt rhBMP clearance.[50]

The package insert for rhBMP describes contraindications for its use, including active infection at the operative site, pregnant women or those planning to become pregnant within one year, patients with a known hypersensitivity to rhBMP or bovine type I collagen, and any patient with an active malignant neoplasm or a history of malignant neoplasm in the vicinity of the proposed surgery. This important oncologic contraindication stems from concerns about the unknown effects of this growth factor on cancer cells. The potential carcinogenic effects of BMPs have been explored, but no definitive link has been established.[50]

At present, there is a greater understanding of the critical functions of BMPs in cancer. BMP-4 was reported to stimulate breast cancer cell invasion and promote bone remodeling. Clinically, Paez-Pereda et al.[51] described the role of BMP-4 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.[52] suggested that BMP-10 suppressed the growth and aggressiveness of malignant cells by inducing apoptosis via a SMAD-independent pathway, which was correlated to the modulation of extracellular signal-regulated kinase and X-linked inhibitor of apoptosis protein. Cao et al.[53] also reported that BMP-4 suppresses breast cancer metastasis by inhibiting myeloid-derived suppressor cell activity in mice. They also suggested that BMP-4 decreases granulocyte-colony stimulating factor secretion via the suppression of nuclear factor-kB activity *(Figure 3)*.

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 BMPs family should not be tested as simply equals. 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 of metastasis in tumor microenvironment. 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.[18]

A report published by the FDA described BMP-2-induced adverse effects such as bone resorption, local inflammation, ectopic bone formation, and cancer; specifically, 86 reports of oral and maxillofacial surgery from 2002 to 2011 were found to display negative outcomes.[54] Recent studies,[12,39] showed increased pathogenicity of oral cancer cell lines after transient exposure to rhBMP. This is a significant consideration since the majority of segmental bone defects in the head and neck region are caused by resection of OSCC.[39]

However, off-label use of rhBMP-2 and rhBMP-7 has been attempted in some cases to solve particularly significant reconstructive challenges in the craniomaxillofacial skeleton.[4] Desai et al.[6] described the use of rhBMP-2 in six patients with significant mandibular defects secondary to traumatic injury or neoplasms. In addition, Zhou et al.[43] performed gene microarray analysis with quantitative polymerase chain reaction in 25 oral tongue squamous cell carcinomas and found that increased BMP-2 gene expression was associated with regional lymph node metastasis and extracapsular spread.

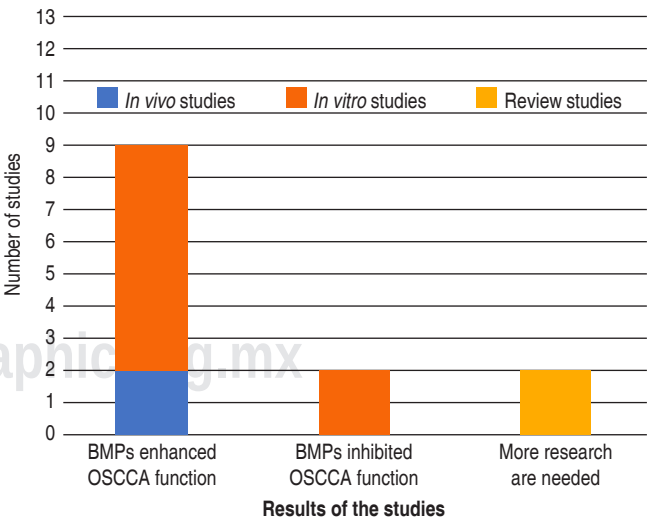

Figure 3: *Role of BMPs in oral squamous cell carcinoma (OSCC) studies in the literature.*

Based on this, the authors believe that rhBMPs should not be used for reconstruction of mandibular defects originating from OSCC.

Kokorina et al.[39] developed a laboratory investigation using six human OSCC cell lines, with three cell lines having baseline gene expression of BMP-2 and three cell lines without baseline gene expression of BMP-2, in order to determine if rhBMP-2 has biological effects on the invasiveness of human OSCC cell lines. They concluded that rhBMP-2 has an adverse biological effect on invasiveness of human OSCC cell lines *in vitro*. These findings raise concern for the safe application of rhBMP-2 for reconstruction of bone defects in oral cancer patients. Kim et al.[40] discussed the probability of adverse effects caused by 1 mg/ml of rhBMP-2 and they warned that rhBMP-2 induced invasion and progression of pre-existing cancer cells that might not be detected in a diagnostic process. This study also emphasized the importance of the *in vitro* coculture system (cancer cells with fibroblasts) for the evaluation of cancer progression induced by regenerative biomaterials. They considered that malignant tissues near the defective areas should be treated or removed in advance to eliminate the possibility of adverse effects caused by rhBMP-2 in OSCC.

Kokorina et al.,[12] developed an investigation to establish the relevance of the BMPs signaling pathway in human OSCC cell lines and determine if there is a biologic impact of stimulating this pathway with rhBMP-2. They found that exogenous treatment of human OSCC cell lines with rhBMP-2 prior to engraftment in an orthotopic animal model caused the subsequent tumors to be more locally aggressive with worse survival rates. The authors affirmed in their research that caution should be taken when considering the therapeutic use of BMPs for reconstruction of bone defects in oral cancer patients.

Alternatively, a recent report showed that rhBMP-2 did not have any adverse effects on proliferation or angiogenesis in human OSCC cell lines when tested *in vitro* or *in vivo* using an ectopic site animal model.[3] Subsequently, Lappin et al.,[45] investigated the effects of rhBMP-7 on the behavior of oral keratinocytes and human OSCC cells *in vitro*. They found that rhBMP-7 exhibited significant dose-related inhibitory effects on the doubling time and viability of cancer cells, but not on the proliferation or viability of oral keratinocytes. These authors affirmed that in cell culture, rhBMP-7 exerts antineoplastic effects. However, Jin et al.,[38] studied 29 oral carcinomas by immunohistochemistry and found that BMP-2/4, BMP-5 and BMP type IA receptors were expressed in 73%, 73%, and 83% of tumors, respectively. They concluded that the BMPs pathway is involved in carcinogenesis of oral epithelium.

As reflected in the literature, the role of BMPs in the OSCC is poorly understood and the research in this regard is contradictory. BMPs affect not just human OSCC cells but also the surrounding tumor microenvironment, including tumor microvasculature and immune cells.[55] Gao et al.,[3] despite stating that rhBMP-2 did not have any adverse effects on proliferation or angiogenesis in human OSCC cell lines, affirmed that further studies are needed before using rhBMP-2 for bone tissue engineering in oral cancer-related skeletal defects. All these findings further contribute to contraindicating the use of BMPs to reconstruct maxillofacial bone defects in the vicinity of a resected tumor or in patients undergoing treatment for malignancy.

To elucidate the physiological roles of BMPs in OSCC, it is extremely important to analyze a large number of materials simultaneously by using the latest high-throughput technologies. These high-throughput analyses may prove valuable for elucidating the context-dependent roles of BMPs in a comprehensive manner and must be performed in order to better understand the potential roles these molecules may have in OSCC tumorigenesis and metastasis.

Conclusion

Although a relationship between BMPs and cancer has been noted for over 20 years, the precise roles of BMPs signaling in cancer development and progression are just beginning to be elucidated. Depending on the BMPs ligand and cancer type, BMPs can either promote or inhibit tumorigenesis. According to the data collected by us, we do not recommend its use to reconstruct maxillofacial bone defects caused by resection of OSCC. This review serves to further clarify the role of exogenous BMPs in OSCC and shed light on the recent development and use of small molecule BMPs in maxillofacial reconstructions.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60 (5): 277-300.
2. Goldenberg D, Lee J, Koch WM, Kim MM, Trink B, Sidransky D, et al. Habitual risk factors for head and neck cancer. Otolaryngol Head Neck Surg. 2004; 131 (6): 986-993.
3. Gao Q, Tong W, Luria JS, Wang Z, Nussenbaum B, Krebsbach PH. Effects of bone morphogenetic protein-2 on proliferation and angiogenesis in oral squamous cell carcinoma. Int J Oral Maxillofac Surg. 2010; 39 (3): 266-271.
4. Chenard KE, Teven CM, He TC, Reid RR. Bone morphogenetic proteins in craniofacial surgery: current techniques, clinical experiences, and the future of personalized stem cell therapy. J Biomed Biotechnol. 2012; 2012: 601549.
5. Patel R, McCluskey S, Goldstein D, Minkovich L, Irish J, Brown D, et al. Clinicopathologic and therapeutic risk factors for perioperative complications and prolonged hospital stay in free flap reconstruction of the head and neck. Head Neck. 2010; 32 (10): 1345-1353.
6. Desai S, Sclaroff A, Nussenbaum B. Use of recombinant human bone morphogenetic protein 2 for mandible reconstruction. JAMA Facial Plast Surg. 2013; 15 (3): 204-209.
7. Hogan BL. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. Genes Dev. 1996; 10 (13): 1580-1594.
8. Massagué J. TGFβ signaling: receptors, transducers, and mad proteins. Cell. 1996; 85 (7): 947-950.

9. Schliephake H. Bone growth factors in maxillofacial skeletal reconstruction. Int J Oral Maxillofac Surg. 2002; 31: 469-484.
10. Burkus JK, Gornet MF, Dickman CA, et al. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002; 15: 337-349.
11. Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. J Bone Joint Surg. 2001; 83 (suppl 1): 151-158.
12. Kokorina N, Lewis J, Zakharkin S, Krebsbach P, Nussenbaum B. rhBMP-2 has adverse effects on human oral carcinoma cell lines *in vivo*. Laryngoscope. 2012; 122 (1): 95-102. doi: 10.1002/lary.22345.
13. Thawani J, Wang A, Than K, Lin C, La Marca F, Park P. Bone morphogenetic proteins and cancer: review of the literature. Neurosurgery. 2010; 66: 233-246.
14. Jin H, Pi J, Huang X, Huang F, Shao W, Li S, et al. BMP2 promotes migration and invasion of breast cancer cells via cytoskeletal reorganization and adhesion decrease: an AFM investigation. Appl Microbiol Biotechnol. 2012; 93 (4): 1715-1723.
15. Liu J, Ben QW, Yao WY, Zhang JJ, Chen DF, He XY, et al. BMP2 induces PANC-1 cell invasion by MMP-2 overexpression through ROS and ERK. Front Biosci (Landmark Ed). 2012; 17: 2541-2549.
16. Park Y, Kang MH, Seo HY, Park JM, Choi CW, et al. Bone morphogenetic protein-2 levels are elevated in the patients with gastric cancer and correlate with disease progression. Med Oncol. 2010; 27: 1192-1199.
17. Feeley BT, Gamradt SC, Hsu WK, Liu N, Krenek L, et al. Influence of BMPs on the formation of osteoblastic lesions in metastatic prostate cancer. J Bone Miner Res. 2005; 20: 2189-2199.
18. Bach DH, Park HJ, Lee SK. The dual role of bone morphogenetic proteins in cancer. Mol Ther Oncolytics. 2017; 8 :1-13.
19. Carter TG, Brar PS, Tolas A, Beirne OR. Off-label use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for reconstruction of mandibular bone defects in humans. J Oral Maxillofac Surg. 2008; 66 (7): 1417-1425.
20. Raida M, Clement JH, Leek RD, Ameri K, Bicknell R, Niederwieser D, et al. Bone morphogenetic protein 2 (BMP-2) and induction of tumor angiogenesis. J Cancer Res Clin Oncol. 2005; 131 (11): 741-750.
21. Clement JH, Raida M, Sanger J, et al. Bone morphogenetic protein 2 (BMP-2) induces *in vitro* invasion and *in vivo* hormone dependent growth of breast carcinoma cells. Int J Oncol. 2005; 27: 401-407.
22. Langenfeld EM, Calvano SE, Abou-Nukta F, et al. The mature bone morphogenetic protein-2 is aberrantly expressed in non–small cell lung carcinomas and stimulates tumor growth of A549 cells. Carcinogenesis. 2003; 24: 1445-1454.
23. Langenfeld EM, Langenfeld J. Bone morphogenetic protein-2 stimulates angiogenesis in developing tumors. Mol Cancer Res. 2004; 2: 141-149.
24. Kleeff J, Maruyama H, Ishiwata T, et al. Bone morphogenetic protein 2 exerts diverse effects on cell growth *in vitro* and is expressed in human pancreatic cancer *in vivo*. Gastroenterology. 1999; 166: 1202-1216.
25. Horvath LG, Henshall SM, Kench JG, et al. Loss of BMP2, Smad8, and Smad4 expression in prostate cancer progression. Prostate. 2004; 59: 234-242.
26. Sulzbacher I, Birner P, Trieb K, et al. The expression of bone morphogenetic proteins in osteosarcoma and its relevance as a prognostic parameter. J Clin Pathol. 2002; 55: 381-385.
27. Orui H, Imaizumi S, Ogino T, et al. Effects of bone morphogenetic protein-2 on human tumor cell growth and differentiation: a preliminary report. J Orthoped Sci. 2000; 5: 600-604.
28. Asano N, Yamakazi T, Seto M, et al. The expression and prognostic significance of bone morphogenetic protein-2 in patients with malignant fibrous histiocytoma. J Bone Joint Surg Br. 2004; 86: 607-612.
29. Buckley S, Shi W, Driscoll B, et al. BMP4 signaling induces senescence and modulates the oncogenic phenotype of A549 lung adenocarcinoma cells. Am J Physiol Lung Cell Mol Physiol. 2004; 286: L81-L86.
30. Ro TB, Holt RU, Brenne A, et al. Bone morphogenetic protein-5, -6, and -7 inhibit growth and induce apoptosis in human myeloma cells. Oncogene. 2003; 23: 3024-3032.
31. 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.
32. Raida M, Sarbia M, Clement JH, et al. Expression, regulation and clinical significance of bone morphogenetic protein 6 in esophageal squamous cell carcinoma. Int J Cancer. 1999; 83: 38-44.
33. Ong DB, Colley SM, Norman MR, et al. Transcriptional regulation of a BMP-6 promoter by estrogen receptor alpha. J Bone Miner Res. 2004; 19: 447-454.
34. Haudenschild DR, Palmer SM, Moseley TA, et al. Bone morphogenetic protein (BMP)–6 signaling and BMP antagonist noggin in prostate cancer. Cancer Res. 2004; 64: 8276-8284.
35. Masuda H, Fukabori Y, Nakano K, et al. Increased expression of bone morphogenetic protein-7 in bone metastatic prostate cancer. Prostate. 2003; 54: 268-274.
36. Franzen A, Heldin N. BMP-7 induced cell cycle arrest of anaplastic thyroid carcinoma cells via p21 and p27. Biochem Biophys Res Comm. 2001; 285: 773-781.
37. Yang WH, Lan HY, Tai SK, Yang MH. Repression of bone morphogenetic protein 4 by let-7i attenuates mesenchymal migration of head and neck cancer cells. Biochem Biophys Res Commun. 2013; 433 (1): 24-30.
38. Jin Y, Tipoe G, Liong E, Lau T, Fun P, Leung K. Overexpression of BMP-2/4, -5 and BMPR-IA associated with malignancy of oral epithelium. Oral Oncology. 2001; 37 (3): 225-233.
39. Kokorina N, Zakharkin S, Krebsbach P, Nussenbaum B. Treatment effects of rhBMP-2 on invasiveness of oral carcinoma cell lines. Laryngoscope. 2011; 121 (9): 1876-1880. doi: 10.1002/lary.21914.
40. Kim MJ, Kim KM, Kim J, Kim KN. BMP-2 promotes oral squamous carcinoma cell invasion by inducing CCL5 release. PLoS ONE. 2014; 9 (10): e108170.
41. Soares A, Xavier R, Miguel M, Souza L, Pinto L. Bone morphogenetic protein-2/4 and bone morphogenetic protein receptor type IA expression in metastatic and nonmetastatic oral squamous cell carcinoma. Am J Otolaryngol. 2010; 31: 266-271.
42. Xu T, Yu C, Sun J, Liu Y, Wang X, Pi L, et al. Bone morphogenetic protein-4-induced epithelial-mesenchymal transition and invasiveness through Smad1-mediated signal pathway in squamous cell carcinoma of the head and neck. Arch Med Res. 2011; 42: 128-137.
43. Zhou X, Temam S, Oh M, Pungpravat N, Huang, Mao L, et al. Global expression-based classification of lymph node metastasis and extracapsular spread of oral tongue squamous cell carcinoma. Neoplasia. 2006; 8 (11): 925-932.
44. Sand J, Kokorina N, Zakharkin S, Lewis J, Nussenbaum B. BMP-2 expression correlates with local failure in head and neck squamous cell carcinoma. Otolaryng Head Neck. 2014; 150 (2): 245-250.
45. Lappin D, Abu-Serriah N, Hunterc K. Effects of recombinant human bone morphogenetic protein 7(rhBMP-7) on the behaviour of oral squamous cellcarcinoma: a preliminary *in vitro* study. Brit J Oral Max Surg. 2015; 53: 158-163.
46. Koehler S, Purmessur D, Iatridis J, Hecht A, Qureshi S, Cho S. Does BMP-2 really cause cancer? A systematic review of the literature. Spine J. 2012; 12: 81S-98S. http://dx.doi.org/10.1016/j.spinee.2012.08.252
47. Skovrlj B, Koehler S, Anderson P, Qureshi S, Hecht A, Iatridis J, et al. Association between BMP-2 and carcinogenicity. Spine. 2015; 40 (23): 1862-1871.

48. Herford A, Cicciu M. Recombinant human bone morphogenetic protein type 2 jaw reconstruction in patients affected by giant cell tumor. J Craniofac Surg. 2012; 21 (6): 1970-1975.
49. Wang K, Inman J, Hayden R. Modern concepts in mandibular reconstruction in oral and oropharyngeal cancer. Curr Opin Otolaryngol Head Neck Surg. 2011; 19: 119-124.
50. Fisher M, Yee K, Alba B, Tanna N, Bastidas N, Bradley J. Applications of bone morphogenetic protein-2: alternative therapies in craniofacial reconstruction. J Craniofac Surg. 2019; 30 (7): 1952-1959.
51. Paez-Pereda M, Giacomini D, Refojo, D, Nagashima A, Hopfner U, Grubler Y, et al. Involvement of bone morphogenetic protein 4 (BMP-4) in pituitary prolactinoma pathogenesis through a Smad/estrogen receptor crosstalk. Proc Natl Acad Sci. 2003; 100: 1034-1039.
52. Ye L, Kynaston H, Jiang W. Bone morphogenetic protein-10 suppresses the growth and aggressiveness of prostate cancer cells through a Smad independent pathway. J Urol. 2009; 181: 2749-2759.
53. Cao Y, Slaney C, Bidwell B, Parker B, Johnstone C, Rautela J, et al. BMP4 inhibits breast cancer metastasis by blocking myeloid-derived suppressor cell activity. Cancer Res. 2014; 74: 5091-5102.
54. Woo EJ. Recombinant human bone morphogenetic protein-2: adverse events reported to the Manufacturer and User Facility Device Experience database. Spine J. 2012; 12: 894-899.
55. Jiramongkolchai P, Owens P, Hong CC. Emerging roles of the bone morphogenetic protein pathway in cancer: potential therapeutic target for kinase inhibition. Biochem Soc Trans. 2016; 44 (4): 1117-1134.
56. Ehata S, Yokoyama Y, Takahashi K, Miyazono K. Bi-directional roles of bone morphogenetic proteins in cancer: another molecular Jekyll and Hyde? Pathol Int. 2013; 63 (6): 287-296.
57. Cooper G, Kou T. Risk of cancer after lumbar fusion surgery with recombinant human bone morphogenic protein-2 (rh-BMP-2). Spine. 2013; 38 (21): 1862-1868.
58. Davies SD, Ochs MW. Bone morphogenetic proteins in craniomaxillofacial surgery. Oral Maxillofac Surg Clin North Am. 2010; 22 (1): 17-31.

Conflict of interest: All the authors declare that they have no conflict of interest.
Funding: No funding was received for conducting this research.

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