Investigational New Drugs (2022) 40:1322–1332
https://doi.org/10.1007/s10637-022-01298-4

REVIEW

BMP2 as a promising anticancer approach: functions and molecular mechanisms

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Received: 9 July 2022 / Accepted: 22 August 2022 / Published online: 30 August 2022

Summary

Bone morphogenetic protein 2 (BMP2), a pluripotent factor, is a member of the transforming growth factor-beta (TGF-β) superfamily and is implicated in embryonic development and postnatal homeostasis in tissues and organs. Experimental research in the contexts of physiology and pathology has indicated that BMP2 can induce macrophages to differentiate into osteoclasts and accelerate the osteolytic mechanism, aggravating cancer cell bone metastasis. Emerging studies have stressed the potent regulatory effect of BMP2 in cancer cell differentiation, proliferation, survival, and apoptosis. Complicated signaling networks involving multiple regulatory proteins imply the significant biological functions of BMP2 in cancer. In this review, we comprehensively summarized and discussed the current evidence related to the modulation of BMP2 in tumorigenesis and development, including evidence related to the roles and molecular mechanisms of BMP2 in regulating cancer stem cells (CSCs), epithelial-mesenchymal transition (EMT), cancer angiogenesis and the tumor microenvironment (TME). All these findings suggest that BMP2 may be an effective therapeutic target for cancer and a new marker for assessing treatment efficacy.

Keywords BMP2 · TGF-β, SMAD · CSCs · EMT · TME

Introduction

The transforming growth factor β (TGF-β) superfamily is an evolutionarily conserved group of proteins with similar structural characteristics that are considered to appear from the early life history stage of multicellular (metazoan) evolution [1, 2]. The TGF-β superfamily has more than 30 members, including TGF-1, activin, nodal, and bone morphogenetic proteins (BMPs), and they can bind to different receptors, including activin-like kinases (ALKs), TGF-beta receptors (TGFBRs), and BMP receptors (BMPRs) [3]. BMPs were first discovered in 1965 for their ability to cause ectopic bone formation [4]. Subsequently, several studies indicated that BMP signaling is established as an organism develops and plays an important role in early embryogenesis, neural development, and retinal development [5–7]. A large amount of recent evidence emphasizes the relationship between cancer and BMP family members, BMP antagonists, and BMP receptors [8–10]. In addition, BMPs widely regulate various signaling molecules that may regulate crucial events in tumor growth, metastasis, and tumor angiogenesis via diverse signaling pathways [11, 12]. Based on gene homology, protein structure, and function, BMP members have been further divided into seven subgroups: BMP-2/4, BMP-3/3b, BMP-5/6/7/8/8b, BMP-9/10, BMP-11/growth, BMP-12/13/14 and BMP-15/GDF9 [13–15]. In mechanistic analysis, disulfide bonds covalently link two monomers of BMP molecules to form mature molecules that regulate normal physiological development and several diseases [16, 17]. Within the BMP family, BMP2 has been widely studied for its functions in osteogenic differentiation, chondrogenic differentiation, and endochondral ossification in stem cells and mesenchymal tissue [18–20]. In oncology research, bone

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marrow-derived mesenchymal stem cells (BM-MSCs) are vital precursors of tumor stromal cells [21]. These results suggest that the potential role of BMP2 in cancer development deserves further elucidation [22].

The functions of the other family members have been extensively investigated. The detailed information is shown in Table 1. The function of TGF-β family members is highly associated with the regulation of fibrosis, immune responses, chondrogenesis, osteogenic differentiation, and cancer. Throughout history, cancer has been one of the biggest threats to human health and life and one of the major causes of death [23]. Fortunately, cancer therapy research has made great progress in recent years, providing patients with various new treatments. Molecular targeted therapy has been a real breakthrough in the treatment of cancer patients in recent years. Genes and proteins involved in cancers could be potential targets for the development of molecular targeted therapy. The functions and molecular mechanisms underlying the anticancer potential of BMP2 are included in this review.

Table 1 Names and functions of TGF-β family proteins

Protein name	Official symbol	Functions
TGF-β1	TGFB1	Fibrosis [24], recovery after intracerebral hemorrhage [25], skeletal muscle regeneration [26], immune regulation [27], cancer [28, 29], chondrocyte dedifferentiation [30], atherosclerosis [31], nervous system development [32], cardiac remodeling [33], Alzheimer's disease [34], diabetic nephropathy [35], atopic asthma [36]
TGF-β2	TGFB2	Glucose and fatty acid metabolism [37], biliary-derived liver diseases [38], fibrosis [39], cancer [40, 41], regulating human hair cycle [42], extracellular matrix production in human trabecular meshwork cells [43], severe asthma [44], cartilage development and diseases [45], ameliorating osteonecrosis of the femoral head [46], activating proliferative scar fibroblasts [47], glaucomatous eyes [48], diabetic retinopathy [49]
TGF-β3	TGFB3	Regulation of immune responses [50], cancer [51], cerebral ischemia−reperfusion injury [52], chondrogenesis [53], osteogenic differentiation [54]
Inhibin α	INHA	Follicle-stimulating hormone secretion [55], cancer [56–58], inhibiting osteogenic differentiation [59]
Inhibin β	INHB	Follicle-stimulating hormone secretion [55], cancer [60, 61], oxytocin secretion [62], metabolic disease [63]
Nodal	NODAL	Human placental development [64], cancer [65]
Myostatin	MSTN	Negatively regulates skeletal muscle cell proliferation and differentiation [66]
BMP-2	BMP2	Bone and cartilage development [67, 68], cancer [69]
BMP-3	BMP3	Suppressing osteoblast differentiation [70], negatively regulates bone density [71], fibrosis [72], cancer [73]
BMP-4	BMP4	Stimulated osteoprotegerin synthesis in osteoblasts [74], cancer [75], arterial stiffness and carotid atherosclerosis in patients with type 2 diabetes [76]
BMP-5	BMP5	Primary chondrocyte proliferation and cartilage matrix synthesis [77], sympathetic neuron dendritic growth [78], nephrosclerosis [79]
BMP-6	BMP6	Osteogenic differentiation [80], iron homeostasis [81], cancer [82], ovulation [83]
BMP-7	BMP7	Fibrosis [84], inflammation [85], callus remodeling [86], osteogenesis [87], cancer [88], kidney tissue development [89]
BMP-8	BMP8	Thermogenesis in brown adipose tissue [90]
BMP-9	GDF2	Idiopathic pulmonary arterial hypertension [91], fibrosis [92], cancer [93], osteogenic and angiogenic differentiation [94]
BMP-10	BMP10	Cardiovascular development [95], cancer [96]
GDF-1	GDF1	Congenital cardiovascular malformations [97]
GDF-3	GDF3	Cancer [98], embryonic development [99], myogenic cell fusion [100]
GDF-5	GDF5	Osteoblastic differentiation [101], white adipose tissue thermogenesis [102], osteoarthritis [103], Parkinson's disease [104]
GDF-6	GDF6	Normal formation of some bones and joints [105], ocular developmental anomalies [106]
GDF-7	GDF7	Cancer [107], osteogenic differentiation [108]
GDF-9	GDF9	Ovarian function [109]
GDF-9B	BMP15	Ovarian function [109]
GDF-10	GDF10	Neural repair after stroke [110], cancer [111]
GDF-11	GDF11	Anti-Aging [112], cancer [113, 114], neuroprotection [115]
GDF-15	GDF15	Growth control [116], metabolic diseases [117], fibrosis [118], cachexia [119], cancer [120], aging [121]
MIS	AMH	Fertility [122]
Lefty A	LEFTY2	Left–right asymmetry determination of organ systems [123], cancer [124]
Lefty B	LEFTY1	Left–right asymmetry determination of organ systems [123], cancer [125]

There are two types of BMPRs: type I BMP receptors (BMPIRs: BMPRIA, BMPRIB, and ActRI) and type II BMP receptors (BMPIIRs: BMPRII, ActRII, and ActRIIB). Studies have indicated that the expression of BMPRIA, BMPRIB, and BMPRII is related to tumor grade in human prostate cancer tissues [126]. In addition, the protein expression levels of BMPRIA, BMPRIB, and BMPRII were significantly higher in B-cell chronic lymphocytic leukemia (B-CLL) cells than in normal cells. In particular, BMPRIA and BMPRIB were significantly upregulated in B-CLL patients with the advanced-stage disease [127]. BMP or BMPR mutations have been demonstrated in neoplasms in additional studies [128]. Thus, fully addressing the effects of BMPs in cancer is urgently needed. BMP2 is a candidate growth factor that has been approved by the Food and Drug Administration (FDA) for bone and cartilage repair and regeneration [129]. Abnormal activation of BMP2 can be detected in osteoarticular diseases [130]. It is worth noting that BMP2 signaling promotes non-small cell lung cancer bone metastases [131]. Recent studies have also highlighted the possible relationships of BMP2 with malignant cancer transformation, growth, and metastasis. We discuss the relevant findings next.

BMP2 signaling

TGF-β signal transduction is usually divided into SMAD (small mother against decapentaplegic)-dependent classical pathways and nonclassical pathways that are independent of SMAD in most instances [131]. The TGF-β family comprises several members, and we used the TGF-β subfamily as an example to demonstrate the process of the TGF-β/SMAD signaling cascade. The initiation of TGF-β/SMAD signaling is mediated by the binding of TGF-β ligands to its transmembrane TGF-β receptors, which include TGF-β type 1 receptor (TGF-βR1) and type 2 receptor (TGF-βR2) [132]. First, TGF-β ligands binding to TβRII form a heterodimeric that recruits and activates TβRI by phosphorylating specific serine and threonine residues. Then, activated TβRI phosphorylates SMAD proteins (SMAD2 and SMAD3) at C-terminal serine residues and forms phosphorylated heterodimers. Extracellular signals are transmitted intracellularly. SMAD proteins act as the intracellular transducers of TGF-β signals and are grouped into three major classes: receptor-regulated SMADs (R-SMADs, e.g., SMAD1, SMAD2, SMAD3, SMAD5, SMAD8, and SMAD9), common SMADs (Co-SMAD, e.g., SMAD4), and inhibitor SMADs (I-SMAD, e.g., SMAD6, SMAD7) [133]. In the cytosol, SMAD4 is a common binding target for SMAD2/SMAD3, which stabilizes the structure of SMAD2/SMAD3 phosphorylated heterodimers by forming a trimeric complex. Subsequently, the trimeric complex is transported into the nucleus, cooperating with other DNA-binding transcription factors, to regulate target gene expression [134, 135]. Additionally, I-SMADs may inhibit R-SMAD function by competing with SMAD4 for R-SMAD binding [136]. Similar to TGF-β/SMAD signaling, BMPs also activate SMAD proteins by relying on the binding of BMP ligands to type I and II BMP receptors in transmembrane signaling. Notably, the downstream targets of BMP receptors are SMAD1/SMAD5/SMAD8, which form multimers with SMAD4 for transport into the nucleus and regulate the transcription of target genes by BMP responsive elements (BREs) [137, 138] (Fig. 1). The target genes of BMP2/SMADs include some key proteins that induce osteogenic differentiation, angiogenesis, and signaling molecules to regulate other signaling pathways and networks [139, 140]. BMPRIA is the most effective receptor for BMP2 among the three types of I receptors [141]. Studies have shown that BMP2/BMPRIA/SMAD signaling can upregulate the expression of the Wnt inhibitors Dkk1 and Sost in osteoblasts [142]. In addition to canonical SMAD-dependent signaling, several SMAD-independent downstream signaling pathways, including classic mitogen-activated protein kinase (MAPK) pathways and the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [143–145], have also been reported.

BMP2 functions and molecular mechanisms in cancer

Early studies of BMP2/SMAD signaling mainly focused on the effect of inducing bone and cartilage formation [146, 147]. With the in-depth study of BMP2 and the molecular biological mechanism of tumorigenesis, the role of BMP2 in tumorigenesis has attracted increasing attention. Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/index.html) is a web server for cancer and normal gene expression profiling and interactive analyses based on t samples from the TCGA and GTEx databases. Differential expression analysis of BMP2 was performed on cancerous and para-cancerous tissues from the GEPIA database, as presented in Fig. 2, implicating an important role for BMP2 in cancer. Further investigations will be reviewed to clarify the detailed mechanism.

Cancer stem cells (CSCs)

CSCs constitute a special subpopulation in cancer and are inherently present in cancer cell populations. With the ability to self-renew and produce heterogeneous cancer cells, CSCs are key drivers of processes of malignant cancer progression, such as metastasis, chemoresistance, and recurrence [148]. BMP2 can be used as a marker and promote the differentiation of stem cells into chondrogenic and osteogenic tissues

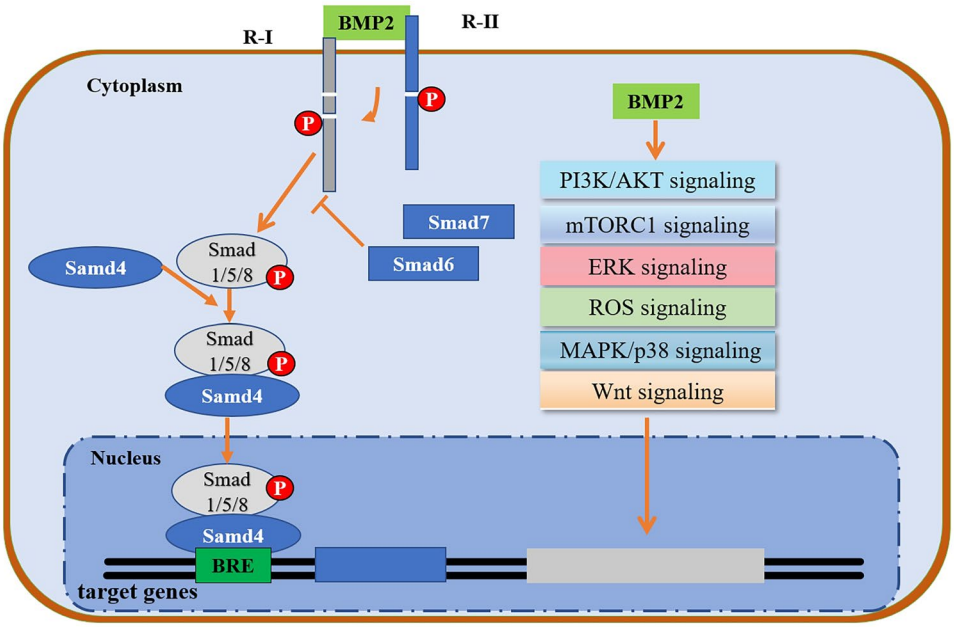

Fig. 1 BMP2 signaling

[129]. Studies have demonstrated that BMP-2 can decrease the tumorigenicity of CSCs with high aldehyde dehydrogenase activity in the human osteosarcoma cell line OS99-1 by reducing the expression of embryonic stem cell markers (Oct3/4, Nanog, and Sox-2) and inducing the transcription of osteogenic markers (Runx-2 and Collagen Type I) [149,

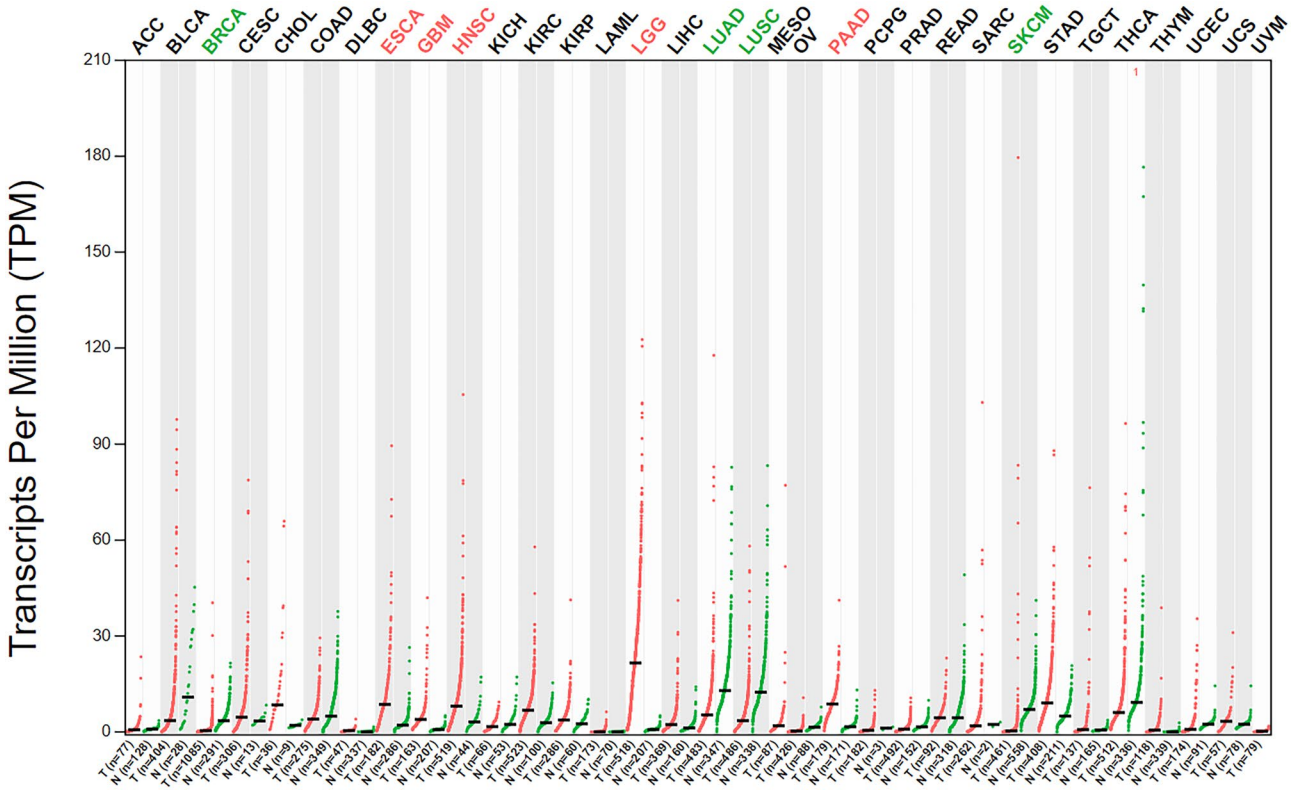

Fig. 2 Gene expression profiles across all tumor samples and paired normal tissues from the GEPIA database (T: tumor, N: normal). Dot plot. Each dot represents the expression of BMP2 in a sample

150]. BMP-2 also weakened the tumor-initiating ability of human renal cancer stem cells by initiating bone formation [151]. These results suggest that BMP-2 may provide an opportunity for cancer treatments by inducing differentiation along an osteogenic pathway. Additionally, BMP2 maintains the regulation of stemness features in cancer development. Glioblastoma multiforme (GBM) is characterized by special hypoxic microenvironment centers and partially necrotic cores enriched with stem-like cancer cells that increase the formation of resistant populations. Studies have demonstrated that BMP2 can increase glioblastoma stem-like cell responsiveness to chemotherapy by downmodulating the HIF-1α/MGMT axis [152]. Although intriguing, BMP2 appears to regulate CSCs in a contradictory manner. BMP2 signals also contribute to the emergence of cancer stem cells. In breast cancer, BMP2 induces epithelial-mesenchymal transition (EMT) and stemness through Rb and CD44 [153, 154]. In colon cancer, BMP-2 induces cancer cell metastasis by regulating STAT3-mediated EMT and/or CSC marker expression [155]. In addition, BMP2 signaling activity can be detected in mesenchymal stem cells (MSCs) [156]. Bone MSCs have the ability to promote cancer growth and stem cell niche formation [157]. The regulatory mechanism is summarized in Fig. 3.

EMT

EMT refers to the process by which epithelial cells transform into mesenchymal cells [158]. Physiologically, epithelial cells are normally associated tightly with their adjacent cells via adherent junctions, tight junctions, and desmosomes. They also maintain apical-basal polarity and contact that inhibits their potential to dissociate from the epithelial layer [159]. Although mesenchymal cells are located adjacent to epithelial cells, they are loosely packed and lack polarity and intercellular junctions, which allows them to migrate through the extracellular matrix [160]. Epithelial cells transformed into mesenchymal cells may lose their connection and polarity, change their morphology, and enhance their migration ability, thus gaining invasion and metastasis abilities [161]. Early studies pointed to the fact that BMP2 induces EMT and invasion in colon cancer by activating the PI3K/Akt pathway [145, 162]. Similarly, BMP2 induces the mTORC1 pathway to promote nasopharyngeal carcinoma cell proliferation and invasion [163]. In human pancreatic cancer PANC-1 cells, BMP2 increases EMT-associated protein matrix metalloproteinase-2 (MMP-2) levels through the activation of ROS and ERK signaling pathways [164]. The regulatory mechanism is summarized in Fig. 1.

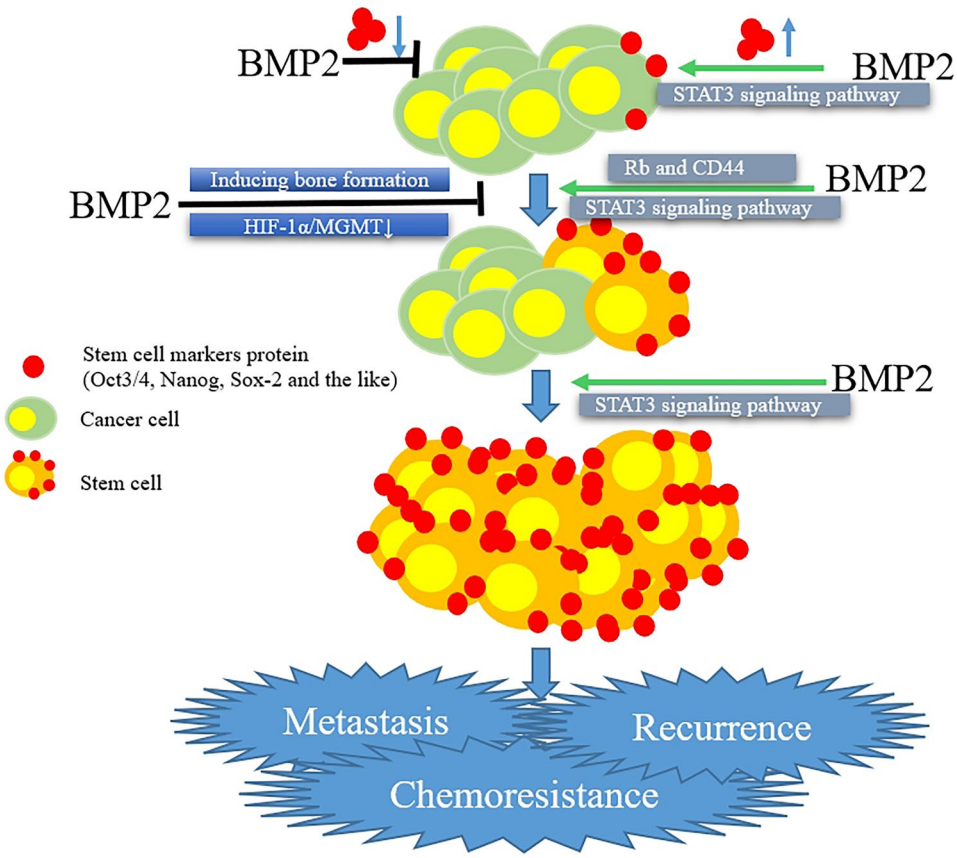

Fig. 3 The regulatory mechanism of BMP2 in CSCs

Angiogenesis

Angiogenesis is essential to maintain the supply of nutrients and oxygen required to support cancer growth. It is difficult for cancers to grow more than 2 mm in diameter without an increased supply of oxygen and nutrients [165]. Studies have indicated that BMP2 expression can be detected in several cancer tissues, and BMP receptors are overexpressed in circulating endothelial progenitor cells (EPCs) and MSCs; all of these factors are involved in cancer angiogenesis [166]. BMP2 overexpression was demonstrated to activate angiogenesis in cancer by inducing the phosphorylation of SMAD 1/5/8 and ERK-1/2. ERK-1/2 activation increased the expression levels of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and angiogenin, which all mediate cellular responses in endothelial cells. The inhibitor of DNA binding 1 (Id1) protein, which promotes angiogenesis, is the direct downstream effector of SMAD 1/5/8 [167]. In addition, a positive correlation between VEGF and BMP2 has been confirmed in lung cancer patients [168]. In an in vitro experiment, coculture with the hepatocellular carcinoma cell line HepG2 enhanced the angiogenic ability of endothelial cells via the BMP2-mediated MAPK/p38 signaling pathway [169]. Given its pivotal role in cancer angiogenesis, BMP2 has been termed a potential target for the inhibition of cancer angiogenesis. Thus, BMP2 also has an anticancer effect on some natural compounds. For instance, linalool inhibited the angiogenic activity of endothelial cells by activating ERK-mediated BMP2 deregulation [170]. An arabinogalactan from flowers of Panax notoginseng may reduce the migratory activity and tube formation ability of endothelial cells by inducing BMP2/SMAD/Id1 signaling [171]. The heparan sulfate (HS) mimetic WSS25 also inhibits cancer angiogenesis by blocking BMP2/SMAD/Id1 signaling [172]. The regulatory mechanism is summarized in Fig. 1.

Microenvironment

The influence of the TME on tumor cell behavior emphasizes the important relationship between the environment and cancer cell origin, growth, or metastasis. TME factors not only include carcinoma tissue structure, function, and metabolism but also include the intrinsic environment of cancer cells [173]. Overexpression of various growth factors and cytokines can be detected in the TME, and this phenotype is mediated by cancer cells via autocrine, paracrine, and juxtracrine mechanisms [174]. An increase in BMP2 protein levels in diverse TME has been detected, particularly in luminal cancers. Studies have indicated that high levels of BMP2 signaling mediated by the receptor BMPR1B promote the transformation of immature human mammary epithelial cells into luminal cancer-like cells, which could be related to the effect of BMP2 in controlling the maintenance and differentiation of early luminal progenitors [175].

Recent studies have found that several carcinoma-associated mesenchymal stem cells (CA-MSCs) are recruited to and aggregate in the TME and promote cancer growth by increasing the number of CSCs. Notably, on the basis of expressing traditional MSC markers, CA-MSCs have a characteristic expression profile distinguished from MSCs in healthy individuals, and this profile includes BMP2. In a human ovarian carcinoma model in vitro, BMP2 augmented the effects of CA-MSCs on tumorigenesis and cancer stem cells [176]. In the bone microenvironment, BMP2 upregulated the expression of osteogenic markers that facilitated MSC transformation into osteosarcoma with the help of WNT signaling [177]. The underlying mechanism of high BMP2 expression in the TME may be attributed to intratumoural acidosis [178]. The regulatory mechanism is summarized in Fig. 1.

As innate immune cells of the myeloid lineage, macrophages have diverse capacities, including phagocytosis (such as pathogens, cell debris, foreign substances, microbes, and cancer cells), antigen presentation, and immunomodulation [179]. Tumor-associated macrophages (TAMs) are macrophages that infiltrate the TME and are major components of the tumor immune system [180]. Immune function regulation by BMP2 signaling is dependent on the microenvironment. In the inflammatory response, BMP2 is known as a chemoattractant for lymphocytes, monocytes, and macrophages [181]. In liver cancer, high levels of BMP2 can aggravate cancer growth by regulating immune cells in the TME [182]. In turn, several immune cell types are important regulators of BMP2. Studies have indicated that macrophages produce BMP2 in the process of bone healing [183]. A similar mechanism was detected in TAMs. In breast cancer, BMP2 has been demonstrated to be a driving force implicated in breast microcalcification formation; it is secreted by TAMs in the TME but not by the breast cancer cells themselves [184]. Therefore, BMP2 acts as a linker between the microenvironment and carcinogenesis, and cancer patients may benefit from treatments targeting BMP2.

Conclusions and perspective

Among the BMP family members, BMP2 is one of the most heavily studied. BMP2 protein can promote bone formation, similar to other BMPs that are well known as osteogenic growth factors. The biology of BMP2 has recently gained attention in a wide range of research fields, especially in cancer, resulting in the expansion of scientific understanding around this protein. In this review, we discuss the roles of BMP2 in cancer, which may be associated with

transcriptional activation and signal transduction. Studies have also suggested that BMP2 plays roles in several characteristic processes that contribute to cancer progressions, such as those related to CSCs, EMT, cancer angiogenesis, and the TME. Moreover, BMP2 mediates multiple signaling pathways, including SMAD-dependent and SMAD-independent pathways, many of which are carcinogenic. The most noteworthy finding is that BMP2 has dual roles in cancer development. On the one hand, BMP2 can inhibit the expansion of several malignant cancer stem cell subpopulations by inducing chondrogenic differentiation, osteogenic differentiation, and endochondral ossification. On the other hand, BMP2 can promote tumorigenesis and development by mediating cancer-related gene regulation and signal activation. Nevertheless, a range of cancer patients may benefit from BMP2 inhibition.

BMP2 and BMP2-associated signaling pathways play a variety of roles in cancer based on current studies in molecular biology and model organisms. It is highlighted that the conflicting data on BMP2 indicate a demand for additional meticulous studies. For example, BMP2 acts as a tumor suppressor that inhibits CSC expansion by reducing the expression of embryonic stem cell markers and inducing the transcription of osteogenic markers in cancer progression. In contrast, BMP2 acts as an oncogene by inducing EMT and CSC formation. BMP2 also augments the effects of CA-MSCs on tumorigenesis and CSCs. In summary, published studies have suggested that BMP2 is essential for tumor development, and paradoxical effects have been observed. A therapeutic strategy aimed at BMP2 can only be developed after the role of BMP2 has been clarified.

Acknowledgements We thank all participants involved in this research.

Author's contributions Tongtong Li, Yongwei Lai and Xu Han wrote the main manuscript. Tongtong Li, Yongwei Lai, Xu Han, and Xin Niu compiled Figs. 1, 2, and 3. Pengxia Zhang was responsible for proofreading.

Funding This work was supported by the National Natural Science Foundation of China (No. 21777060), the Horizontal Project of Jiangsu Medical Vocational College (jcyxhxkt2021-01), and the Biology Discipline Team (jdxktd-2019003).

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, informed consent was not needed.

Conflicts of interest All authors declare no conflicts of interest.

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