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An Update of Bone Morphogenetic Proteins as Biomarker and Therapy for Cancer

Chandi C Mandal[1*] **and Md Mizanur Rahman** [2]

[1]*Department of Biochemistry, School of Life Sciences, Central University of Rajasthan, Rajasthan, India*
[2]*Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA*

***Corresponding author:** Dr. Chandi C Mandal, Department of Biochemistry, School of Life Sciences, Central University of Rajasthan, NH-8, Bandarsindri, Kishangarh-305817, Ajmer, Rajasthan, India, Tel:+919650569396; Fax : +911463238772; E-mail ID: chandicmandal@gmail.com

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Introduction

Inspite of doing extensive research work, cancer is still the leading cause of deaths. Its associated cost accounts a largest economic burden worldwide. Cancers are perhaps the most complicated diseases, since each tumor and/or a subpopulation of tumor cells may have a distinct type of genetic alteration, gene mutation, oncogenic signaling, metabolic features, epigenetic changes and also receive different multiple signals from local environment [1-7]. Cancer forming cells acquire many characteristics resembling to embryonic stem cells. For example, cancer initiating cells (cancer stem cells) and embryonic stem cells, both prefer glycolytic mechanism indicating a similar type of metabolic reprogramming [7,8]. Certain genetic alteration and the signals of tumor microenvironment may promote epigenetic switching which may be responsible for aggressiveness of cancers. Most poorly differentiated cancer cells express many embryonic transcription factors such as Snail, Twist, Zeb1, Sox2 and also modulate expressions of many microRNAs (such as miR-200c, miR-34a, miR-302-367, let-7a) which play crucial role in embryogenesis, and they undergo epithelial to mesenchymal transition (EMT) and regain at least in part their embryonic features [6,9,10]. Increased mesenchymal features in epithelial cancer cells make them more invasive, survival during transportation through blood circulation, extravasation from blood vessels, and survival at premalignant sites [6]. However, this increased mesenchymal characteristic does not support their growth at pre malignant sites, until they again undergo mesenchymal to epithelial transition (MET). In fact, disseminated cancer cells at premalignant site need to adjust with the new environment by accepting circumstantial signaling which may lead to develop a distinct type of epigenetic switching, resulting in conversion of EMT to MET, and eventually develop macro-metastasis [6]. Thus, dysregulation of such protein, which regulates embryogenesis or organogenesis may cause tumorigenesis and metastasis. Abnormal expressions of bone morphogenetic proteins (BMPs) which play critical role in embryogenesis, cartilage, and bone formation have been found in various types of cancers, which have been linked with tumorigenesis and metastasis of many cancer types [11-15]. However, the role of BMPs in tumorigenesis still remains a debate [16].

BMPs are a group of proteins which are known to be potent growth factors and morphogens of the TGFβ superfamily. BMPs transduce intracellular signaling cascades by both canonical and non-canonical pathways [12,17]. In canonical pathway, BMPs transduce their signals by binding with serine/threonine protein kinase receptors, followed by forming heterotetrameric complex of receptor type 1 and 2. This heterotetrameric complex when activated upon phosphorylation, phosphorylates regulatory receptor substrates R-Smads (Smad1, Smad5 and Smad8), which binds to co-Smad, Smad4 which also transduces TGFβ signaling, and subsequently undergoes nuclear translocation and regulate gene transcription with aid of other co-activator/co-repressor [12,17]. All BMPs usually mediate their signaling cascade following this basic mechanism. However, BMP-2 and BMP-4 first bind to receptor type I to make complex with receptor type II, whereas BMP-6 and BMP-7 first interact with type II to form complex by recruiting type I [12,18]. Therefore, these differences may generate distinct types of intracellular signaling. In non-canonical pathways, BMPs may activate various types of signaling such as PI3K/AKT, MAPKinase, p38 etc. [13,19-25]. Moreover, several signaling (e.g., Wnt signaling) cross talk to BMP pathway to modulate its functional activity [26]. Our earlier studies have established that BMP-2 activates PI3K/AKT signaling via ROS generation [20]. Moreover, shutting down of PI3K/AKT activity prevents BMP-2 driven Smad binding activity to the promoters of osterix and colony stimulating factor 1 (CSF1) to inhibit osteoblast and osteoclast activity respectively [21,22]. Thus, non-canonical signaling pathways work independently and also modulate the canonical pathway. Therefore, detail molecular understanding of BMP signaling is required to explain the functional activity of BMPs in various cell types including cancer cells.

Bone Morphogenetic Proteins and Cancer

Dysregulation of several types of BMPs (e.g., BMP-2, BMP-4, BMP-6 and BMP-7) have been reported in various cancer tissues [11,13,27-32]. Many research studies through cell culture, animal and human studies have done to investigate the link between BMPs and cancer. The results obtained from different independent research groups are very complex, largely varied in cancer types and very fluctuating from one BMP type to other. Although findings are contradictory, researchers still believe that it might have a dual role in tumorigenesis, similar to TGFβ [16]. For example, BMP-2 decreases cell proliferation of most cancer types such as colorectal, hepatocellular and osteosarcoma [33-36]. Although, inhibitory effect of BMP-2 on breast cancer growth and proliferation is not much convincing [37, 38], similarly it also has no effect on prostate cancer growth [39]. However, studies support a tumorigenic role of BMP-2 in lung cancer [28,40]. Recent evidences also strongly indicate the positive role of BMP-2 on invasiveness of many cancers, such as gastric, bladder, pancreatic, oral, prostate and breast cancer [13,14,23,41-46]. Expression of BMP-2 in cancer tissues often correlates with lymph node metastasis and bone metastasis [11,13,28]. Similarly, expression of BMP-2 in ovarian cancer tissues positively correlates with poor survival of ovarian cancer patients [11]. BMP-2, and BMP-6 increase

the growth of renal cell carcinoma and castration resistant prostate cancer [49,50]. In contrast, they inhibit cell proliferation of some cancers such as breast and myeloma [38,47,48]. BMP-6 also inhibits breast cancer cell migration and invasion [51,52]. In contrast, it increases migration and invasion of prostate cancers [53]. Prostate cancer tissues contain high levels of BMP-6 whereas its expression was found to be low in breast cancer tissues [27,47]. However, BMP-7 often inhibits proliferation and invasion of cells of many cancer types such as breast, prostate, kidney and lung cancers [54-56]. Moreover, xenograft study reveals the inhibition of osteolytic metastasis of breast cancer MDA-MB-231 cells in response to BMP-7 treatment [31]. BMP-7 may also increase tumor dormancy at the metastatic site by increasing senescence of prostate cancer stem cells [57]. In addition, decreased BMP-7 expression in breast cancer tissues is associated with bone metastasis [31] but, BMP-7 positive tumors correlate with bone metastasis [30]. Similarly metastatic prostate cancer cells contain increased level of BMP-7 and it is further increased in case of castration resistant prostate cancers [55]. These raise a question for use of BMP-7 as anticancer therapy.

Molecular mechanism of BMPs in regulation of EMT/MET and metastasis

Canonical BMP-Smad signaling is often found to be active in many cancers. In addition, BMP-2 signaling may also activate non-canonical PI3K/AKT, MAPKinase, NFκB [13,23,24,58] and also increases matrix mettaloproteinases (MMP-2 and MMP-9) activity which could be responsible for the invasion of cancer cells [13,23]. Recent literature evidences that BMP-2 treatment inhibits epithelial marker E-cadherin and promotes mesenchymal protein vimentin resulting in EMT of several cancer types such as gastric cancer, pancreatic cancer and lung cancer [23,24,41]. However, BMP-6 and BMP-7 may inhibit EMT of cancer cells such as breast, cholangio carcinoma, and melanoma cancer [52,59,60]. Most studies reported that BMP-7 inhibits TGFβ-induced EMT of cancer cells. In this note, we have discussed earlier that TGFβ and BMPs both use Smad4 to transduce Smad signaling. Thus, it could be the case that the addition of BMPs may use some Smad4 which was used by TGFβ signaling to inhibit TGFβ-driven EMT. BMPs work through both autocrine and paracrine fashion. Thus, the aberrant amount of BMPs present in the microenvironment of primary tumor site may promote EMT, a crucial feature of cancer invasiveness. Further research study is needed to know the role of BMPs in MET at the metastatic site, since MET is also crucial for the outgrowth of metastases. Thus, the contextual signals originating in the microenvironment near to metastases are very important in the conversion of EMT to MET [6]. This idea indicates that local signals might have a distinct impact at the metastatic site from its primary site. These signals might modulate different types of intracellular signaling cascades of cancer cells by discrete types of epigenetic changes.

BMPs as potential biomarkers

Abnormal expression of an embryonic gene or factor could lead to develop tumorigenesis and metastasis. Similarly, abnormal expression patterns of BMPs have been found in many cancer tissues as compared to control tissues. Recent studies document an elevated level of serum BMP-2 in advanced gastric cancer patients when compared to control or early stage of cancer patients [61,62]. It was found that level of BMP-2 is positively correlated with lymph node metastasis, depth of cancer invasion and grade of tumor histology [62]. Similarly, the serum BMP-2 level is positively associated with stage of lung cancers and metastasis of lung cancer patients [63,64]. Moreover, decreased level of BMP-2 correlates with increased overall survival of lung cancer patients [63]. The serum BMP-2 level was found to be higher in multiple myeloma patients than that of healthy control [65]. Likewise, high expression of BMP-2 in ovarian cancer tissues predicts the shorter survival of cancer patients [11]. Moreover, therapy responding patients show a decreased level of serum BMP-2 as compared to therapy non-responders, suggesting levels of BMP-2 as a therapy efficacy marker [64]. Thus, the serum BMP-2 could be a diagnostic and prognostic marker for cancer patients. Many extensive researches are needed to determine whether serum BMP-2 can be used for all cancer types or cancer specific. Thus, the levels of other BMPs such as BMP-6, BMP-7, and BMP-4 along with BMP-2 could predict cancer progression and metastasis more efficiently. In future, molecular characterization of BMP signaling networks present in cancers and determining the serum BMPs profile could be a powerful tool to achieve better diagnosis and prognosis of cancer patients.

In summary, BMPs especially BMP-2 may prevent cell proliferation and induce apoptosis of cancers at early stage of cancers, but it might induce metastasis by promoting EMT of epithelial cancers at a later stage of cancers. Recent literature suggests a positive link of microcalcification (seen in breast and other cancers) and invasiveness of cancers [66,67]. Therefore, BMPs might promote physiologic microcalcification in cancer tissues when epithelial cancer cells acquire both osteoblastic property and EMT characteristics [68,69]. Thus, disruption of BMP-2 signaling might be a novel therapeutic strategy for cancer treatment. Therefore on the basis of the above discussion, we propose that the combination of BMP-2 inhibitor with an anti-proliferating agent might be a better option to prevent cancer growth and metastasis.

This note just insights an idea, but future study will confirm this concept.

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