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Osteopontin: An Effector and an Effect of Tumor Metastasis

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Abstract

Osteopontin (OPN) is a matricellular protein that is produced by multiple tissues in our body and is most abundant in bone. It is also produced by cancer cells and plays a determinative role in the growth, progression and metastasis of cancer. Clinically, OPN has been reported to be upregulated in tumor cells *per se*; this is also reflected by increased levels of OPN in the circulation. Thus, increased OPN levels in the plasma are an effect of tumor growth and progression. Functionally, high OPN levels are determinative of higher incidence of bone metastases in mouse models and are clinically correlated with metastatic bone disease and bone resorption in advanced breast cancer patients. Several research efforts have been made to therapeutically target and inhibit the activities of OPN. In this article we have reviewed OPN in its role as an effector of critical steps in tumor progression and metastasis, with a particular emphasis on its role in facilitating bone metastasis of breast cancer. We have also addressed the role of the host-derived OPN in influencing the malignant behavior of the tumor cells.

Keywords

Osteopontin; cancer; bone; metastasis; secreted phosphoprotein 1

Metastasis is a complicated process that involves several steps, including detachment from the primary tumor, penetration of the extracellular matrix (ECM), survival in the circulatory system, extravasation, attachment at the site of metastasis, and establishment of a microenvironment conducive to growth [1–6]. There is evidence suggesting that the protein product of the proto-oncogene, osteopontin (OPN) may play a role in each critical step of the process of metastasis. OPN, an acidic phosphoglycoprotein, with an arginine-glycine-aspartate (RGD) integrin-binding motif, is a member of the SIBLING (Small integrin-binding ligand N-linked glycoproteins) family which includes five members of secreted proteins that can modulate cell behavior by autocrine as well as paracrine mechanisms by their interaction with cell surface receptors such as integrins [7]. OPN protein is a monomer, ranging in length from 264 to 301 amino acids that undergoes extensive posttranslational modification; including phosphorylation, glycosylation, and cleavage, resulting in molecular mass variants ranging from 25 to 75 kDa. OPN contains a hydrophobic leader sequence characteristic of a secreted protein, a potential calcium phosphate apatite binding region of consecutive asparagine residues, a cell attachment GRGDS sequence, a thrombin cleavage site, and two glutamines that are recognized substrates for transglutaminase-supported

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multimer formation [8–11]. Through the receptor binding motifs on itself and its receptors, OPN mediates cell-matrix and cell-cell communication [12–14]. Integrin binding with OPN brings about clustering and activation of focal adhesion complexes. These comprise a number of regulatory and structural proteins like FAK, src and other cytoskeletal proteins [15–19]. As a consequence several signal transduction pathways are turned on which culminate in change of cellular properties like adhesion, proliferation, migration and survival (Fig. 1).

OPN can exist as an immobilized extracellular matrix molecule in mineralized tissue and/or in an intracellular, perimembranous location. Intracellular OPN is part of a hyaluronan-CD44-ERM (ezrin/radixin/moesin) attachment complex involved in fibroblast, macrophage, and tumor cell migration, suggesting that OPN stimulates or participates in motogenic activity of cells [20–22]. OPN also exists as a cytokine in body fluids. OPN has also been found on epithelial cells and in secretions of the gastrointestinal tract [23], kidneys [24, 25], thyroid [26], breast [27–30], uterus [25], placenta [31–35], and testes [34, 35]. OPN is also expressed by leukocytes [36–38], smooth muscle cells [36–38], and highly metastatic cancer cells [39–53].

OSTEOPONTIN IN THE CLINIC - AN EFFECT OF TUMOR METASTASIS

While OPN is expressed by several cell types and functions in a variety of physiological roles, OPN expression is upregulated in tumor cells. Clinical studies have also revealed a correlation between plasma OPN, tumor burden and prognosis in patients with breast cancer metastasis [54–67]. Abundant secretion of OPN acts as a marker for advanced breast cancer and multiple cancer histotypes [56–67]. The level of plasma OPN in patients with breast cancer is higher compared with levels in plasma from controls (Fig. 2). Since OPN is expressed by both tumor infiltrating lymphocytes as well as the tumor cells themselves, OPN expression specifically within the tumor cells correlated with patient survival (86–96). Studies have shown a correlation between OPN and the progression and severity of multiple cancers, including breast [63, 68–71], colon [72, 73], lung [73, 74], and prostate [40, 75]. OPN has repeatedly been shown to be present at high levels in the circulation of patients with metastatic cancers [55, 70, 75–78] and in tumors with increased metastatic potential [75, 79–82], thus making it relevant in the context of studying its expression in the perspective of metastasis. The levels of OPN in the plasma of patients with breast cancer are significantly higher in those with bone metastasis compared to those who do not have bone metastasis [75, 83]. Moreover, this level of OPN increases with time, as the disease progresses. Among these women, those with highest levels of OPN (more than 2.5 µg/ml) show poor survival compared to those with OPN levels between 1.1–2.5 µg/ml (Fig. 3). Whether the circulating OPN impacts ‘homing’ of breast cancer cells to bone is still not known.

Alternate splicing of the OPN message yields three messages, OPN-a, OPN-b and OPN-c. The Weber laboratory [84] have identified that the isoform OPN-c, is selectively expressed in invasive, but not in non-invasive, breast tumor cell lines, and it effectively supports anchorage independence. They have further showed in a cohort of 178 breast specimens, that OPN-c is expressed in 78% of cancers, 36% of surrounding tissues and 0% of normal

tissues. When correlated with tumor grade, the staining for OPN-c increased from grade 1 to grade 3. Their study reported that in conjunction with HER-2, OPN-c could reliably predict grade 2–3 breast cancer. Thus, it is likely that OPN-c may have diagnostic value when coupled with a conventional panel of breast cancer biomarkers.

OPN AS AN EFFECTOR OF TUMOR METASTASIS

Overall OPN signaling acts to enhance malignancy by giving the cells a survival/growth advantage. OPN also augments attributes that confer increased aggressiveness by activating expression of genes and functions that contribute to metastasis [14, 85–90]. As summarized below, tumor cell-derived OPN orchestrates several key steps in tumor development and progression; it does so by changing the microenvironment of cancer cells and temporally and spatially facilitating the critical events that regulate the malignant behavior of the tumor cells. We have used the bone as a site of culmination of the cascade of events that a metastatic breast cancer cell goes through (Fig. 4). Discussed below are 6 critical events in tumor progression and metastasis that are influenced by tumor cell-derived OPN.

Prevention of Apoptosis

Tumor cells are distinct from normal cells in that they lack the fine balance between proliferation and apoptosis. Changes reported in most of the molecular players in the apoptotic signal cascade attest to the strong selective pressure during tumor progression for the ability of cancer cells to resist apoptotic cell death [91]. In fact, this acquired ability of cancer cells is an essential trait in tumor progression. Research from our laboratory showed that depletion of OPN from cancer cells abrogates their ability to form tumors, under experimental conditions, in athymic nude mice [92]. Under experimental conditions, overexpression of OPN caused activation of Akt *via* phosphorylation of Akt at Ser 473 and endowed cancer cells with the ability to resist the stress of growth under serum starvation conditions [19]. Cook *et al.* [85] have reported that OPN also likely activates the Akt pathway by mediating the upregulation of GAS6, ultimately resulting in evasion of apoptosis. As documented by Lee *et al.*, the interaction of OPN with its receptor CD44 activates inside-out signaling mediated by Src. This confers enhanced ability to resist and survive u.v. induced apoptosis [93].

Recruitment of Tumor Vasculature

The continued growth of the tumor is dependent on the recruitment and establishment of a vascular supply. The association of OPN with this process is a consequence of its ability to bind the $\alpha v \beta 3$ integrin which is expressed in neovascular endothelial cells [94]. OPN plays a key role in vascular repair and regeneration and also upregulates the expression of VEGFs. Experimentally, constitutive overexpression of OPN in murine neuroblastoma cells induced neovascularization *in vivo* [95–99]. OPN has also been reported to upregulate the expression of two members of the CCN (CTGF/Cyr61/NOV) family, cysteine-rich angiogenic inducer 61 (CYR61) and connective tissue growth factor (CTGF). CYR61 has functionally been demonstrated to enhance neovascularization and tumor growth *in vivo* (in model systems) [85]. It is likely that both, OPN and CYR61 act *via* the $\alpha v \beta 3$ receptors on the surface of endothelial and tumor cells to enhance vascularization. Khan *et al.* reported that OPN

prevents apoptosis in endothelial cells *via* NF- κ B [100]. OPN seems to play a role in the formation of the lumen during the neovascularization process as well [101]. In bone, soluble (tumor-derived) OPN plays a vital role in the establishment of vasculature by mediating adhesion to endothelial cells, co-operating with VEGF, and preventing apoptosis of the endothelial cells [96, 99, 102–105].

Adhesion and Migration of Tumor Cells

Usually cells adhere to OPN *via* integrins. Aberrant integrin expression on cancer cells allows them to chemotactically migrate towards OPN. Breast cancer cell lines migrate toward OPN [106–108], and increasing OPN expression in these cells often correlates with increased Matrigel invasiveness. Conversely, studies including our own have shown that cells that are deficient for OPN expression often display decreased motility when compared to their OPN-expressing counterparts [20, 92, 109]. OPN-mediated migration can involve numerous integrins, including α v β 1, α v β 5 [110, 111], α 4 β 1 [112], α 9 β 1 [113], α 8 β 1 [114]. However, the integrin heterodimer most commonly associated with the malignant properties of OPN is α v β 3 [94, 115–117]. This integrin is invariably expressed in bone metastases while its expression is variable in primary breast tumors [118]. The human metastatic cancer cell line, MDA-MB-435 [119–122] produces copious amounts of OPN and migrates towards OPN *via* the α v β 3 integrin, while the two non-metastatic human breast cancer cell lines, 21PT and 21NT that do not express α v β 3, use α v β 1, and α v β 5 integrins [123]. Certain splice variants of the cell surface proteoglycan CD44 (CD44v3-v6) can also bind OPN in an RGD-dependent manner [124, 125]. The role of CD44 in influencing cancer cell behavior was demonstrated by Gunthert and colleagues who reported that overexpressing CD44v6 is sufficient to induce full metastatic behavior in pancreatic tumor cells that are normally nonmetastatic [126]. And conversely, fibroblasts from OPN^{-/-} mice have defective CD44-dependent adhesion and migration [20]. In fact, the β 1 integrin can influence the behavior of cancer cells to spread and migrate when OPN is bound by CD44 variants [127]. The integrin-induced migration of cells in response to OPN is mediated by the growth factor pathways involving HGF, its receptor Met and EGF [123, 128]. Specifically, OPN-integrin induced cell migration was accompanied by an initial increase in Met kinase activity, followed by an increase in the protein levels of c-Met [123]. There is also evidence to suggest that OPN may impact cell motility *via* its interactions with focal adhesion complexes (FAC) [16, 129]. Thus, OPN plays a direct role in influencing the behavior of cancer cells by participating in several cell migration pathways.

Invasion of Extracellular Matrix

In order to penetrate its underlying basement membrane a tumor needs to be able to produce the necessary proteases, often members of the matrix metalloproteinase (MMP) family. OPN seems to be capable of increasing the cells' production of several proteases. Philip *et al.* [130] demonstrated that treatment of murine melanoma cells with human OPN increased levels of membrane type 1 MMP, pro-MMP2, and active MMP2. MMP2 is capable of degrading some components of the ECM and correlates with invasiveness and metastasis [131]. Breast cell lines that were either transfected or treated with OPN developed increased expression and activity of urokinase-type plasminogen activator (uPA) [107]. uPA is capable of directly or indirectly converting plasminogen to plasmin and activating MMP-1, -2, -3,

–9, and –14 [57, 132, 133], each of which digests specific ECM components while nearly all play role in cancer invasion and metastasis. Over-expression of uPA in rat prostate cancer cells was enough to increase bone metastasis [134]. The upregulation of uPA and MMP-2 by OPN is mediated by integrin linked kinase (ILK) and AP-1 signaling during tumor cell invasion. The ability of OPN to cause proteolysis is further enhanced by thrombin cleavage of OPN. The thrombin cleaved COOH terminal fragment of OPN binds cyclophilin C to the CD 147 cell surface receptor and enhances ECM proteolysis *via* activation of Akt1/2 and MMP-2 [135]. Thus, OPN signaling activates a multitude of events that enable cancer cells to degrade the ECM and escape from the primary site.

Evasion of Host Defense

The journey from primary tumor to site of distant metastasis is a perilous one and only a very small percentage of cells survive. A cell must be capable of persisting in an anchorage-independent state and evading the immune system. There is experimental evidence supporting a role for tumor cell-derived OPN in both areas. Breast tumor cells expressing OPN are capable of anchorage-independent growth as determined in soft agar assays [136]. Conversely, abrogating the expression of OPN retards the ability of breast cancer cells to grow under-anchorage-independent conditions [92]. Breast cancer cell lines, such as MCF7, become more resistant to apoptosis when OPN is bound to its cell surface $\alpha_v\beta_3$ integrin [137]. This anti-apoptotic effect has also been seen in epithelial cells, vascular smooth muscle cells, hemopoietic cells, and immune cells [138–142]. The OPN-dependent resistance to apoptosis can span several different stress conditions. OPN inhibits the inducible nitric oxide synthase (iNOS) in infiltrating immune cells blocking certain tumoricidal functions of these cells [143–145]. Recently, Wai *et al.* [145], blocked OPN in a murine colon adenocarcinoma cell line, and detected an increase in macrophage iNOS expression along with increased NO-mediated tumor cell apoptosis. OPN is also capable of binding factor H, thus protecting tumor cells from complement-mediated lysis [146]. Taken together this shows tumor-derived OPN would provide a strong immune avoidance advantage to tumors capable of its expression, which may more than compensate for the increased levels of immune cells that will be attracted to the OPN present in the tumor.

Growth at the Secondary Site (Bone)

We have exemplified this critical step using the bone as the secondary site since metastasis to the bone is the most catastrophic complication of breast cancer, occurring in 60–83% of advanced breast cancer patients [147–149]. A tumor cell that possesses the ability to hijack the normal cycle of bone production and resorption would have a survival advantage. Once the invading tumor cell has reached its final destination in the bone, it must create the proper microenvironment in which to survive and develop into a viable tumor. The metastases, just as in the primary tumor, require sufficient blood flow to provide oxygen and nutrients and remove waste products to enable the extensive growth of tumors. OPN and parathyroid hormone-related peptide (PTHrP) are the two proteins secreted by cancer cells that are primarily implicated in the disruption of the normal cycle of bone formation and resorption. OPN may play a vital role in the process of establishing growth at a secondary site. As an initial step of colonizing the bone, when breast cancer cells arrive in bone, they first interact with the bone marrow endothelial cells before invading into the bone marrow compartment

[150]. Thus, in order to understand the repercussions of OPN ablation on early steps bone colonization, we assessed the surrogate indicator of heterotypic attachment to human bone marrow endothelial cells (hBME). It was very interesting to see that the MDA-MB-435 tumor cells stably silenced for OPN (OPNi clones) display a strikingly reduced ability to attach to hBME cells (Fig. 5). Recent reports indicate that OPN-expressing cells produce high levels of hyaluronan synthase 2, an enzyme that synthesizes hyaluronan. It is conceivable that in the absence of OPN and consequently hyaluronan, breast cancer cells are unable to attach to the hBME cells. Thus, OPN appears to function in the early steps of colonizing bone.

OPN may also help generate a favorable growth environment by activating growth factors. As previously mentioned, bone is rich in sequestered growth factors that can be used to promote rapid proliferation of the tumor. The uPA produced in response to OPN is capable of activating some growth factors, including HGF, TGF- β , and bFGF [151–154]. In concert with growth factor receptor pathways, such as EGFR and c-met OPN can accentuate effects of EGF and HGF/scatter factor respectively. Seminal studies by Kang *et al.*, showed that OPN forms a component of a “bone-metastasis signature” of breast cancer cells i.e., breast cancer cells that metastasized to bone had increased OPN expression. Furthermore, OPN functionally enhanced incidence of bone metastases by breast cancer cells in concert with interleukin-11 [155]. Expression of OPN in OPN-negative breast cancer cells increases their predilection to form bone metastasis and OPN knock-out mice display significantly lower incidence of bone metastases [42, 156]. Accordingly, high OPN levels are determinative of higher incidence of bone metastases in mouse models and are correlated with metastatic bone disease and bone resorption in advanced breast cancer patients. Thus, OPN plays a vital role in aiding in the colonization of bone as well as in the establishment of growth at the secondary site.

OPN PRODUCED BY CANCER CELLS IS DIFFERENT FROM HOST-DERIVED OPN

While the detection of OPN in the tumor cells or in circulation has been regardless of the source i.e., whether it is produced by the tumor cells or the host cells, there are distinct differences in the OPN produced by the cancer cells and the OPN produced by the host-cells [41,145, 157–161].

1. While the host-derived OPN is associated with the extracellular matrix, OPN produced by tumor cells is soluble and does not associate with fibronectin or vitronectin [161].
2. The tumor-derived soluble form supports invasiveness and the host-derived aggregated form promotes adhesion.
3. While host-derived OPN acts as a macrophage chemoattractant, tumor-derived OPN is able to inhibit macrophage function and enhances the growth or survival of tumor cells in circulation and thus promotes metastasis [159].

4. OPN expressed by host cells bears a different post-translational modification than that of the cancer cells. The tumor cell-derived OPN is less phosphorylated compared to the OPN expressed by non-transformed cells. In fact, transformation of normal rat kidney cells changes the phosphorylation profile of OPN from a phosphorylated form to a non-phosphorylated form [162]. Similarly, OPN produced by *ras*-transformed fibroblasts is significantly less phosphorylated than OPN produced by osteoblasts [163]. Kazaneki and colleagues have proposed that the tumor-derived, less phosphorylated form of OPN may be more effective at promoting cancer progression, either by increasing anchorage-independence and metastasis, or by protecting the cells from immune response and apoptosis, whereas a more highly modified macrophage-produced OPN would serve as an effective chemoattractant and activate T-lymphocytes to attack the tumor cells [164]. It is likely that phosphorylation may influence OPN's ability to interact and signal *via* its receptors.
5. Transformed rat fibroblasts secrete a form of OPN (62-kDa) that has reduced sialylation than the one secreted by non-transformed cells (69-kDa). The 62-kDa form is compromised for its ability to interact with cell surface receptors. Thus, it is likely that the OPN secreted by oncogenically transformed cells may exploit the lack of OPN-receptor interactions to mediate the malignant behavior of the cells [165].
6. Finally, aggressive breast cancer cells secrete a splice variant of OPN, OPN-c, that protects breast cancer cells from anoikis during anchorage-independent growth [166].

ROLE OF HOST-DERIVED OPN IN FACILITATING TUMOR PROGRESSION AND METASTASIS

The contribution of OPN from the host in the development of tumors was elegantly demonstrated by Crawford and colleagues who chemically-induced squamous carcinoma in wild-type and OPN-deficient mice. They found that tumor growth progressed at a much faster rate in the OPN-deficient mice compared to the wild-type mice; this was likely due to the fact that the tumor-associated stromal cells produced OPN in the wild-type animals that attracted tumoricidal macrophages to the growing tumor, thereby slowing tumor growth at the sites where tumors were induced [159]. On the contrary, Nemoto *et al.* reported that wild-type mice supported the metastatic colonization and growth of melanoma cells better than the OPN-deficient mice upon injection of melanoma cells *via* the intracardiac route, suggesting that host-derived OPN may promote cell attachment of tumor cells, leading to higher capacity of cells to attach to bone [42]. In agreement with this, Chakraborty and others [167] have shown that OPN-null mice showed slower progression of tumor growth in breast cancer model as compared to wild type mice. OPN has been determined to be upregulated in response to hypoxia in head and neck cancer patients. The level of OPN in the plasma reflects the degree of hypoxia of the tumor [168–173] and can serve as a surrogate marker for tumor hypoxia and treatment outcome in head and neck cancer patients.

Hypoxia induces sequence-specific DNA-binding complexes mediated by a ras-activated enhancer (RAE) in the OPN promoter to induce upregulated expression of OPN.

THERAPEUTIC TARGETING OF OPN

Given the plethora of processes that OPN can influence in tumor progression and metastasis, OPN presents as a very relevant therapeutic target. Efforts towards these have been made at multiple levels. OPN has been targeted at the levels of transcription by the use of shRNA [92], siRNA [174], miRNA [175] and anti-sense RNA [176, 177]. Given the fact that RNA stability of OPN may also regulate OPN [178] expression, these strategies present tangible approaches to regulate the availability of OPN protein within the cell.

The naturally occurring oroidin alkaloid, (–)- agelastatin A, inhibits OPN protein expression, reduces beta-catenin protein expression and enhances expression of the cellular OPN inhibitor, Tcf-4.

(–)-Agelastatin A treatment also and reduced anchorage-independent growth, adhesion, and invasion in human breast cancer cell lines [179]. The administration of green tea polyphenols caused a decrease in the levels of OPN in TRAMP mice [180]. This was attributed to reduce levels and activity of NF- κ B, a transcription factor that upregulates OPN expression [92].

Another approach is to modulate the activity of OPN. Proteolytic cleavage of OPN by thrombin increases its biologic activity [106, 181] by opening up the parent OPN molecule into its apparent active conformation [106, 182–185]. Treatment of breast cancer cells with the thrombin-inhibitor, Argatroban, resulted in decreased cell growth, colony-forming ability, adhesion, and migration. The tumor latency of implanted breast cancer cells was increased when the animals were treated with Argatroban. This was accompanied by reduced primary tumor growth and significantly decreased lymphatic metastasis of the breast cancer cells in treated animals, implying the possible use of thrombin inhibitors such as Argatroban as potential therapeutic agents [186].

The use of RNA aptamers targeting OPN appears to be a viable approach in blocking the ability of OPN to bind to its cell surface CD44 and $\alpha(v)\beta(3)$ integrin receptors resulting in decreased signaling *via* PI3K, JNK1/2, Src and Akt, signal transduction pathways. This is manifested as decreased adhesion, migration, and invasion characteristics *in vitro* and decreased local progression and distant metastases *in vivo* [187]. The ability of OPN to enhance the development of osseous metastases was markedly reduced upon treatment of the experimental animals with Staphylococcus aureus extracellular adherence protein (Eap). Eap specifically interacted with recombinant full-length OPN and the 40 kD N-terminal MMP cleavage fragment and prevented the OPN/ $\alpha v\beta$ -integrin interaction [188].

As a contralateral approach to blocking OPN activity or reducing its levels is to block the receptor for OPN. The $\alpha v\beta 3$ integrin appears to play a key role in the development of bone metastasis from breast cancer [189]. Osteoclast activation plays an essential role in the development of bone metastasis. The $\alpha v\beta 3$ integrin mediates the attachment of osteoclasts to bone matrix, and it is overexpressed in bone-residing breast cancer cells. Targeting of the

$\alpha v\beta 3$ integrin has been addressed by some laboratories. In the MDA-MB-435 model, of intracardiac injections, the $\alpha v\beta 3$ integrin appears to play an important role in early events (e.g., arrest of tumor cells) in bone metastasis. Mice treated with the $\alpha v\beta 3$ integrin-selective inhibitor, S247, one week prior to injection of the tumor cells showed a significant, dose-dependent reduction in osseous metastasis [190] suggesting that $\alpha v\beta 3$ inhibitors may be useful in the treatment and/or prevention of breast cancer metastases in bone. Ramos *et al.* [191] have reported the ability of a novel $\alpha b\beta 3$ -binding disintegrin, DisBa-01, to inhibit the binding ability of cells to vitronectin and inhibit proliferation, angiogenesis and metastatic ability of cancer cells. These findings are supported by the fact that overexpression of functionally active $\alpha v\beta 3$ integrin in CHO cells drastically increased the incidence, number, and area of bone metastases in nude mice compared with those observed in mock-transfected CHO cells or in CHO cells expressing a functionally inactive $\alpha v\beta 3$ integrin [192]. The MDA-MB-231-BO2 cells established from bone metastasis of MDA-MB-231 cells constitutively overexpress the $\alpha v\beta 3$ integrin. The MDA-MB-231-BO2 cells also show enhanced ability to bind to and invade mineralized bone suggesting that $\alpha v\beta 3$ integrin expression in tumor cells accelerates the development of osteolytic lesions [192].

SUMMARY & FUTURE PERSPECTIVES

The soluble, secreted phosphoprotein, OPN, no doubt influences multiple processes that aid in tumor development and progression and metastasis. Its role in the development of osseous metastasis of breast cancer continues to be elucidated. In its role as a secreted protein, OPN has recently also been reported to influence the growth of indolent tumors [193], leading to the possibility that OPN expression by tumor cells can perturb the systemic environment of the host and support the outgrowth of dormant micrometastases. In doing so, OPN likely influences the hallmark biological programs that dictate tumor progression. Tumor progression in turn, has an escalating effect on the overall levels of circulating OPN. As a secreted protein, OPN has been tapped into as a potential biomarker to indicate tumor metastasis and also as an indicator of response to anti-cancer treatment. New research on the endocrine influences of OPN on dormant or indolent cancer cells prompts the use of OPN as a biologically relevant indicator of precancerous lesions or occult metastases and a reliable predictive indicator of relapse of the disease. This, in turn, will influence the treatment modality and regimens to be adopted. The versatile functions of OPN have made a case for OPN as a therapeutic target and have prompted inquiries into mechanisms to intervene in its expression and activity. Efforts are being made on several fronts to intervene in the action of OPN. This being said, several considerations must be met including making the agents amenable to systemic administration, tolerance to the inhibitory agents and specifically targeting the tumor-derived OPN. This review helps provide an answer to our cover question to conclude that the elevated OPN is both, a cause and an effect of tumor metastasis.

ABBREVIATIONS

bFGF	Basic fibroblast growth factor
CCN	CTGF/Cyr61/NOV family
CTGF	Connective tissue growth factor

CYR61	Cysteine-rich angiogenic inducer 61
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ERM	Ezrin-radixin-moesin
FAC	Focal adhesion complex
FAK	Focal adhesion kinase
hBME	human bone marrow-derived endothelial cells
HGF	Hepatocyte growth factor
ILK	Integrin linked kinase
MMP	Matrix metalloproteases
NF-κB	Nuclear factor κ B
OPN	Osteopontin
PTHrP	Parathyroid hormone-related protein
RAE	Ras-activated enhancer
RGD	Arginine-glycine-aspartate
SIBLING	Small integrin-binding ligand N-linked glycoprotein
TGF-β	Transforming growth factor β
uPA	Urokinase plasminogen activator
VEGF	Vascular endothelial growth factor

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Fig. (1).

Schematic representation of the signaling pathways influenced by osteopontin. The phenotypes manifest as increased ability of cells to proliferate, migrate, survive and influence the development of tumor vasculature.

Fig. (2).

As compared to healthy women, women with metastatic breast cancer have higher median levels of circulating osteopontin.

(Data adapted with permission from Clin Cancer Res 3: 605–611, 1997).

Fig. (3).

(**A**) Temporal increase in the level of plasma OPN in breast cancer patients with metastatic bone disease. (**B**) In patients with bone metastasis of breast cancer, higher OPN plasma levels are associated with poor survival.

(Data adapted with permission from Endocrine-Related Cancer 11:771–779, 2004).

Fig. (4).

Osteopontin plays a role in the critical steps of tumor progression and metastasis. Depicted in this cartoon are the steps in metastasis culminating in colonization at the bone as a secondary site.

Fig. (5). MDA-MB-435 cells that have been stably silenced for osteopontin by RNA interference show decreased heterotypic adhesion to hBME cells.