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Role of osteopontin in the pathophysiology of cancer

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Abstract

Osteopontin (OPN) is a multifunctional cytokine that impacts cell proliferation, survival, drug resistance, invasion, and stem like behavior. Due to its critical involvement in regulating cellular functions, its aberrant expression and/or splicing is functionally responsible for undesirable alterations in disease pathologies, specifically cancer. It is implicated in promoting invasive and metastatic progression of many carcinomas. Due to its autocrine and paracrine activities OPN has been shown to be a crucial mediator of cellular cross talk and an influential factor in the tumor microenvironment. OPN has been implicated as a prognostic and diagnostic marker for several cancer types. It has also been explored as a possible target for treatment. In this article we hope to provide a broad perspective on the importance of OPN in the pathophysiology of cancer.

Keywords

Osteopontin; Matricellular; Cancer; Isoforms; Signaling

1. Introduction

Osteopontin (OPN) is a secreted non-collagenous, sialic acid rich, chemokine-like, matricellular phosphoglycoprotein that facilitates cell–matrix interactions and promotes tumor progression. It is a member of small integrin-binding ligand N-linked glycoproteins (SIBLINGs), a family of five integrin binding glycophosphoproteins. The SIBLING family also encompasses bone sialoprotein (BSP), dentin matrix protein 1 (DMP1), dentin sialophosphoprotein (DSPP), and matrix extracellular phosphoglycoprotein (MEPE). While evidence for a role of BSP and DSPP in cancer is emerging, there is sound data and compelling evidence for OPN in influencing multiple steps in tumor development and metastasis. OPN is known to act through multiple integrins and CD44 and synergize with signaling through EGFR and the HGF receptor, Met. Notably, OPN is expressed by several tissues in the human body; it also is expressed at increased levels by tumor cells from multiple cancer types. OPN being a secreted protein, thus, has been explored for its function and diagnostic or prognostic potential in several cancers. In this review we will discuss the differential roles of host and tumor-derived OPN and the recent advances regarding OPN isoforms, highlight the clinical perspectives on OPN and, summarize the research interrogating multiple avenues to regulate OPN.

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2. Structure of OPN

OPN is a 34 kDa protein that is extensively modified post-translationally; it presents as a 60-kDa phosphoprotein initially called as transformation-associated gene (Craig et al., 1989) and a major sialoprotein in the extracellular matrix of bone (Franzen and Heinegard, 1985). The gene (*SPP1*; *Secreted Phosphoprotein 1*) maps to chromosome 4 (4q13) and contains 7 exons. OPN belongs to a class of proteins that may be referred as Intrinsically Disordered Proteins (IDPs) that constitute a class of biologically active proteins lacking defined secondary and tertiary structure (Kurzbach et al., 2013). Although OPN does not fold into a single defined structure, its conformational flexibility significantly deviates from random coil-like behavior. OPN comprises distinct local secondary structure elements with reduced conformational flexibility and displays distinct tertiary contacts that encompass binding sites for αVβ3 integrin and heparin (Platzer et al., 2011). Moreover, OPN can be cleaved by thrombin, resulting in OPN-R and exposing the cryptic C-terminal _α4β1 and _α9β1 integrin-binding motif (SVVYGLR) (Sharif et al., 2009). OPN bears a polyaspartic acid motif, through which it binds to hydroxyapatite and calcium ions, and an RGD sequence which mediates cell attachment. It is a multifunctional protein and potentially serves as a bridge between cells and hydroxyapatite through RGD [(Arg-Gly-Asp)] integrin-binding sequence and polyaspartic acid, a lymphokine produced by activated lymphocytes and macrophages [thus called as Eta-1 (Early T-Lymphocyte activation gene I)]. It has multiple Ser and Thr phosphorylation sites, sites for N- and O-linked glycosylation, as well as a thrombin cleavage site. Thus, a variety of phosphorylation, glycosylation and sulphation can generate different functional forms of OPN which provide tissue specific and function specific versatility (Sodek et al., 2000). For example, OPN, mutated at three O-glycosylation sites failed to induce the OPN-mediated signaling pathways such as cap-dependent protein translation, NF-κB activity and glucose uptake (Minai-Tehrani et al., 2013b). Thrombin cleavage of OPN facilitates its binding to α4β1, α9β1, and α9β4 integrin receptors (Laffon et al., 1991). OPN gene has an alternative translation start site and thus there are two major variants of OPN, intracellular and extracellular (Suzuki et al., 2002; Shinohara et al., 2008). The structural diversity and consequently the functional complexity get interesting with discoveries of splice variants of OPN (He et al., 2006; Mirza et al., 2008). OPN is subject to alternative splicing, as well as post-translational modifications such as phosphorylation, glycosylation and proteolytic cleavage. These cancer specific splice variants are OPN-a, OPN-b and OPN-c. OPN-b and -c in the blood are biomarkers for distinct cancers. Functional differences have been revealed for different isoforms and post-translational modifications. We have discussed the roles and relevance of these isoforms in detail in the ensuing text.

3. Regulation of OPN

Consistent reports from diverse cancer studies have implied that the presence of OPN in the tumor milieu, irrespective of its source, leads to enhanced tumor growth and metastasis and consequently poor prognosis. Thus, investigations that brought to light different events that cause derailment of the intricate cellular regulation of OPN such as upregulation of transcription by promoter polymorphism, abnormal activation, lack of repressor function and aberrant epigenetic regulation are of specific importance to understand the abnormal

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expression patterns of OPN in cancers. Association of *SPP1* promoter polymorphisms has been documented with several cancers including breast cancer, melanoma and glioma. A detailed study of 241 breast cancer specimens in comparison with DNA from surrounding normal tissue as well as healthy breast samples revealed that the polymorphic site in position −443 of the promoter was associated with tumor grade. This very site, but not others (at −1748 or −1776), showed differences between ER-positive and ER-negative breast cancers and between PR-positive and PR-negative breast cancers, indicating that the *SPP1* promoter SNPs −443 (rs11730582) and −1748 (rs2728127) are important for breast cancer aggressiveness (Ramchandani and Weber, 2013). Melanoma metastases that were homozygous for the −443C allele expressed significantly higher levels of *SPP1* mRNA compared with those that were either heterozygous (−443T/C) or homozygous for the −443T allele. The study also demonstrated binding of c-Myb to the −443 *SPP1* promoter region, which could significantly be enhanced after bFGF stimulation. Thus, differential binding of c-Myb transcription factor at −443 may explain different OPN expression levels in metastatic tumors (Schultz et al., 2009). A different SNP, 155_156GG was found to be significantly associated with an increased risk of glioma. Cellular assays indicated that the transcriptional activity of the *SPP1* promoter containing the −155_156GG allele significantly increased in glioma cells indicating that this variant of *SPP1* promoter might influence the risk of glioma by regulating promoter activity (Chen et al., 2010).

3.1. Activators and repressors

Several signaling pathways when mis-regulated can result in activation of OPN expression. Noteworthy among them are oncogenic, tumor promoting pathways such as receptor tyrosine pathway, G-protein coupled pathways, Wnt/β-catenin, Hedgehog (Hh), NFκβ and estrogen signaling pathways. Several *cis*-regulatory elements have been identified on OPN promoter. One of these is a Ras-activated enhancer (RAE) that binds a protein, the Ras-response factor (RRF), whose ability to form a complex with the RAE is stimulated by Ras signaling in fibroblasts and epithelial cells (Denhardt et al., 2003). Another is the T cell factor-4 (Tcf-4) binding site, which in the *SPP1* promoter can retard OPN transcription when bound by the Tcf-4 protein. The −94 to −24 region of the human *SPP1* promoter is able to bind several known transcription factors, including Sp1, Myc and Oct-1, which may act synergistically to stimulate OPN transcription in malignant astrocytic cells (Denhardt et al., 2003). Up-regulation of aryl hydrocarbon receptor (AhR), a transcription factor activated by xenobiotics, has been observed in lung cancer as well as premalignant lesions (Chuang et al., 2012). AhR positively regulates OPN expression in lung cancer. A positive correlation of OPN and AhR expression in lung cancer specimens was observed. *SPP1* promoter region (−268 to +435) gets activated by both ligand-independent and ligand-activated AhR. This study by Chung et al. suggested that both overexpression of un-induced AhR (in cases of non-smokers with high level of AhR) and ligand-activated AhR (such as in smokers) contribute to up-regulation of OPN (Chuang et al., 2012). Expression of OPN is trans-activated by the Tax protein of HTLV-1 (Chagan-Yasutan et al., 2011). OPN is not only a hypoxiaresponsive gene but also transcriptionally upregulates HIF1α expression under normoxia and hypoxia (Kale et al., 2013; Raja et al., 2013). Studies on colorectal cancer (CRC) showed that OPN is a direct target of estrogen related receptor ERRα (Boudjadi et al., 2013). The critical role of Wnt signaling in regulation of OPN transcription was

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demonstrated by multiple reports (Ravindranath et al., 2011; Mitra et al., 2012). Additional studies have also shown that OPN promoter's responsiveness to β-catenin and Lef-1 was considerably enhanced by Ets transcription factors such as Ets-1, Ets-2, ERM, particularly PEA3 (El-Tanani et al., 2004). NFκβ and the Hh pathway transcription factor Gli1 have also been demonstrated to potently regulate OPN (Samant et al., 2007; Das et al., 2009).

As a counter balance to the activators, to mediate intricate spatiotemporal regulation, there are many repressors that negatively regulate OPN transcription. BRCA1 selectively binds OPN-activating transcription factors estrogen receptor alpha, AP-1, and PEA3 and inhibits OPN promoter transactivation whereas mutant BRCA1 dramatically upregulates OPN protein which also explains the close association of BRCA1 mutation and OPN overexpression in breast cancer (El-Tanani et al., 2006). Breast cancer metastasis suppressor 1 (BRMS1) protein caused a marked (N90%) reduction of *SPP1* mRNA and protein expression. Hedley et al. reported that OPN downregulation by BRMS1 may be responsible, at least in part, for BRMS1-mediated metastasis suppression by sensitizing cancer cells to stress induced apoptosis (Hedley et al., 2008). The El-Tanani lab identified interferon-induced transmembrane protein 3 gene (IFITM3) as a potential protein partner of OPN that reduces OPN mRNA expression and negatively impacts cell adhesion, cell invasion, colony formation in soft agar and preclinical metastasis (El-Tanani et al., 2010). RUNX3 is a transcriptional repressor of OPN and loss of RUNX3 upregulates OPN, which promotes migration in gastric cancer cells (Cheng et al., 2013). Notable repression of OPN is also caused by epigenetic regulators such as miRNA-181a in hepatocellular carcinoma (HCC) cell lines (Bhattacharya et al., 2010) and by hsa-mir-299-5p in breast cancer stem-like cells (Shevde et al., 2010).

4. OPN impacts pathophysiologies of multiple malignancies

In an elegant investigation, Cook et al. identified gene expression changes differentially regulated by OPN in a model of human breast cancer. These changes reflect the six "hallmarks of cancer" in a model of breast cancer progression (Cook et al., 2005). OPN impacts multiple signal transduction events including regulation of Akt, Raf/MEK/ERK signaling (Robertson et al., 2010), ILK/PI3K/GSK-3β (Robertson et al., 2010) and RAN GTPase/c-Met/PI3 kinase (Kurisetty et al., 2008; Yuen et al., 2012). We have outlined below specific events that are triggered by OPN in multiple malignancies. While there seems to emerge a common theme underlying the molecular changes, there are distinct cancer type-specific effects that are mediated by OPN (Fig. 1).

The pattern of isoform expression and post-translational modification is cell-type specific and may influence the potential role of OPN in malignancy and as a cancer biomarker (Anborgh et al., 2011). Invasive breast tumor cells generate three splice variants of OPN, while noninvasive breast cells express only the un-spliced form or no OPN at all. The full-length gene product, OPN-a, induces a gene expression profile associated with tissue remodeling and directed movement/sprouting by invoking signaling through STAT1 and STAT3. This likely upregulates glucose levels in breast cancer cells. It is proposed that the elevated glucose is metabolized by OPN-c dependent signals to generate chemical energy (Shi et al., 2013). Functionally OPN-c supports anchorage-independent growth (Shen and

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Weber, 2013) and induces the expression of oxidoreductases protecting cells from anoikis during anchorage-independent growth (He et al., 2006). While all OPN transcripts promoted local tumor formation of human breast cancer MCF7 cells, when co-cultured with macrophages OPN-c upregulated CD163 levels compared with OPN-a and OPN-b. All OPN transcripts significantly inhibited TNF-α and enhanced IL-10 production by monocytes. This was partly mediated by the upregulated TGF-β1 and MCP-1 production by tumor cells in response to cellular OPN (J. Sun et al., 2013). As the literature on OPN and its variants grows, some discrepancies among reports from different labs will inevitably arise and beg for clarification; for example, the original description of OPN-mediated cellular immunity found IL-10 suppression — at least for macrophage-derived full-length OPN (Ashkar et al., 2000). OPN spliced isoforms were overexpressed in prostate cancer cell lines as compared to non-tumoral prostate cell lines. OPN-c and OPN-b overexpressing cells significantly enhanced xenograft tumor growth and PC-3 proliferation, migration, invasion, soft agar colony formation, and expression of MMP-2, MMP-9, and VEGF. These isoforms supported sustained proliferative survival inducing PI3K signaling. OPN splicing isoforms presented significantly at higher levels as OPN-a, OPN-b and OPN-c transcripts in prostate cancer specimens than in Benign Prostatic Hyperplasia (BPH) specimens. Impressively, ROC curves and logistic regression analyses demonstrated that OPN splicing isoforms and PSA were able to distinguish prostate cancer from BPH patients. The OPN-c isoform was the most upregulated variant and the best marker to distinguish patient groups, presenting sensitivity and specificity of 90% and 100%, respectively. OPN-c protein was also strongly stained in prostate cancer tissues presenting high Gleason score (Tilli et al., 2012b). OPN-a and OPN-b isoforms were expressed in tumor and non-tumor ovarian samples, whereas OPN-c was specifically expressed in ovarian tumor samples. The OPN-c isoform significantly activated OvCar-3 ovarian cancer cell proliferation, migration, invasion, anchorage-independent growth and tumor formation *in vivo* (Tilli et al., 2011). Pancreatic ductal adenocarcinoma (PDAC) is among the malignancies with the worst prognosis. Increased expression of OPN mRNA was found in the tumor cells correlating with increased proliferation and malignant phenotype (Delany, 2010). Nicotine, a risk factor in PDAC, induces an alpha7-nicotine acetylcholine receptor (α7-nAChR)-mediated increase of OPN in PDAC cells. PDAC cells expressed varying levels of OPN-a, OPN-b, and α7-nAChR. Nicotine treatment selectively induced *de novo* expression of OPN-c and increased α7-nAChR expression levels. In PDAC tissue, OPN-c was found in 87% of lesions, of which 73% were smokers (Sullivan et al., 2011). Wu and colleagues have developed a mass spectrometric method to quantify OPN isoforms in human plasma. The method is based on the immunocapture of all OPN isoforms, followed by MRM-MS analysis of isoform-specific tryptic peptides. The results showed that none of the OPN splice variants is cancer specific. However, OPN-a, the major isoform in healthy and non-small cell lung carcinoma (NSCLC) plasma, is substantially elevated in NSCLC patients, whereas OPN-b and OPN-c are at equivalent levels in the two populations (Wu et al., 2012).

Multidrug resistance is a major cause of chemotherapy failure. Recent studies indicate that drug resistance can be rapidly induced by soluble factors, such as cytokines, chemokines, growth factors, and cell adhesion factors in the tumor microenvironment. Data from our laboratory has shown that OPN causes non-classical activation of the developmental Hh

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signaling pathway, leading to nuclear translocation of the GLI1 transcription factor and upregulated expression of ABCB1 and ABCG2 multidrug resistance proteins in a GLI1-dependent manner (Das et al., 2013; Shevde and Samant, 2013). Upregulated expression of the ABC proteins was reflected as resistance of breast cancer cells to doxorubicin and taxol. Hypoxia-induced OPN in prostate tumor cells caused increased mRNA and protein expression of p-glycoprotein (P-gp), a subfamily of ATP-binding cassette transporter in a concentration- and time-dependent manner. Functionally, this was recorded as an increase in the drug efflux activity of the cells. Knockdown of OPN enhanced cell death caused by other drugs, including paclitaxel, doxorubicin, actinomycin-D, and rapamycin, which are also P-gp substrates (Das et al., 2013; I.S. Hsieh et al., 2013).

Multidrug resistance is a feature of mesenchymal cells and is typically acquired after epithelial cancer cells have undergone epithelial-to-mesenchymal transition (EMT) (Li et al., 2013). Evidence from our laboratory directly implicated a functional role for OPN in increasing expression of the mesenchymal markers Twist, Slug, Snail, N-cadherin, Vimentin, and MMP9 concomitant with a loss of Keratin 8/18 and E-cadherin, both of which are associated with an epithelial phenotype (Das et al., 2013). The Kuo lab has reported complementary findings and identified that OPN activates an autocrine MAPK intracellular signaling pathway resulting in Twist activation and Bmi1 expression to further EMT initiation and cell migration (Li et al., 2013). In three distinct but complementary studies OPN knockdown is reported to improve radiobiological effects in MDA-MB-231 cells and to chemosensitize MDA-MB-231 cells to doxorubicin and to CTX by enhancing apoptosis through activation of p38 MAPK signaling (Hahnel et al., 2010; Pang et al., 2011; Yang et al., 2012).

4.1. Non-tumor derived OPN

OPN is expressed in a variety of tissues and bodily fluids, and is associated with multiple pathologies including tissue injury, infection, autoimmune disease and cancer. Thus OPN derived from tumor associated host tissue such as stroma can also impact OPN dependent paracrine effects. OPN is expressed in macrophage cells in multiple pathologies and regulates cytokine expression, expression of inducible nitric oxide synthase, phagocytosis, and migration. While the data is still evolving, the heterogeneity of OPN and its receptors, or of macrophages themselves, might underlie some of the gaps in our knowledge and inconsistencies in the literature (Rittling, 2011). TAMs have multifaceted roles in tumor development, particularly linked with tumor angiogenesis and invasion. In tumor microenvironment, *via* the $\alpha 9\beta 1$ integrin, OPN has been reported to activate TAMs and influence angiogenesis by enhancing cyclooxygenase-2 (COX-2)-dependent prostaglandin E_2 (PGE_2) production. OPN-activated macrophages promote the migration of endothelial and cancer cells *via* PGE2 (Kale et al., 2013). Using a melanoma model, in wild type and OPN knockout mice, Kumar et al. have demonstrated that the absence of host OPN effectively curbs melanoma growth, angiogenesis and metastasis. Host/stromal OPN also regulated the side population phenotype (indicative of stem like drug resistant cells) in murine melanoma cells (Kumar et al., 2010).

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Cells in the tumor microenvironment critically influence the tumor behavior. In particular cancer-associated fibroblasts can promote tumor growth, angiogenesis and metastasis. It has been hypothesized that cancer-associated fibroblasts may be derived from mesenchymal stromal cells that are derived from local or distant sources, such as the bone marrow. Tumor-derived OPN induces production of CCL5 by mesenchymal stromal cells by binding to the integrin cell surface receptors. These activated mesenchymal cells facilitate metastasis of breast cancer cells. This provocative finding provided direct evidence for OPN-induced stromal cell changes culminating in metastasis (Mi et al., 2011).

Alterations in the microenvironment collaborate with cell autonomous mutations during the transformation process. Cancer-associated fibroblasts and senescent fibroblasts stimulate tumorigenesis in xenograft models. The tumor microenvironment undergoes changes concurrent with neoplastic progression. Fibroblasts within premalignant and malignant skin lesions ranging from solar/actinic keratosis to squamous cell carcinoma express OPN. Further investigations from the Stewart lab showed that OPN promotes preneoplastic keratinocyte cellular proliferation and cell survival through the CD44 cell receptor and activation of the MAPK pathway indicating that stromal-derived OPN impacts tumorigenesis by stimulating preneoplastic cell proliferation thus allowing expansion of initiated cells in early lesions (Luo et al., 2011). Cancer incidence increases with aging and is associated with tissue accumulation of senescent cells. Liu and colleagues have elegantly shown that senescent fibroblasts promote neoplastic progression in associated tumors through degradation of fibroblast Tiam1 protein and the consequent increase in secretion of OPN by fibroblasts (Liu et al., 2012).

The effects of primary tumors on the host systemic environment and resulting contributions of the host to tumor growth are poorly understood. Malignant cells may evade death from cytotoxic agents if they are in a dormant state. The host microenvironment plays important roles in cancer progression, but how niches might control cancer cell dormancy is little understood. Boyerinas et al. have reported that OPN secreted by osteoblasts in the endosteal niche anchors leukemic blasts in anatomic locations supporting tumor dormancy. Inhibition of the OPN-signaling axis significantly increased tumor burden in mice and synergized with cell-cycle-dependent Ara-C chemotherapy to reduce detectable bone marrow minimal residual disease (Boyerinas et al., 2013). The Weinberg lab reported that human breast carcinomas instigate the growth of otherwise-indolent tumor cells (micrometastases). This systemic instigation is accompanied by incorporation of bone-marrow cells (BMCs) into the stroma of the distant, once-indolent tumors. BMCs of hosts bearing instigating tumors are functionally activated prior to their mobilization. Secretion of OPN by instigating tumors was found to be necessary for BMC activation and the subsequent outgrowth of the distant otherwise-indolent tumors (McAllister et al., 2008).

Such impact of OPN is also noticed in non-cancer pathophysiologies. For example, in graft-versus-host disease (GVHD) which is a life-threatening complication after allogeneic hematopoietic stem cell transplantation caused by alloreactive donor T cells that trigger host tissue damage. OPN levels are elevated after irradiation and persist throughout the course of GVHD. Blockade of OPN attenuated GVHD with reduced accumulation of donor T cells in

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recipient organs. Amelioration was due to migration and survival suppression caused by anti-OPN treatment on donor-derived T cells (Zhao et al., 2011).

4.2. Tumor-derived OPN

OPN is associated with decreased apoptosis in lung adenocarcinoma (Stemberger et al., 2013). In human lung cancer cells, OPN knockdown suppressed lung cancer cell invasion and metastasis and also induced autophagy and abrogated the radioresistance of the cancer cells (B.S. Sun et al., 2013). Beclin-1 inhibited increase in OPN expression following irradiation leading to enhanced autophagy (Chang et al., 2012). While OPN concentrations were significantly higher in lung cancer patients compared to controls, a negative correlation was detected between OPN and body mass index (BMI), suggesting that in addition to being an indicator of systemic inflammation in lung cancer patients, OPN may also be an indicator of weight loss (Karadag et al., 2011).

OPN regulates malignant transformation of endometrial cancer (Ramachandran et al., 2013). In cervical cancer cells OPN regulates CD44-mediated p38 phosphorylation that induces NF-κB-dependent expression of furin, an extracellular protease implicated in human papilloma virus (HPV) processing that enhances cervical cancer cell motility (Kumar et al., 2010).

The small calcium-binding protein S100A4 promotes angiogenesis, regulation of cell death, cell motility and invasion. S100A4 induces NF-κB-dependent expression and secretion of OPN in a selection of osteosarcoma cell lines. OPN was determined to be an important mediator of the effect of the pro-invasive and metastatic effect of S100A4 (Berge et al., 2011).

Thrombin-cleaved fragments of OPN are overexpressed in malignant glial tumors and provide a molecular niche with survival advantage (Yamaguchi et al., 2013). In glioma cells, overexpression of OPN induced angiogenesis of endothelial progenitor cells *via* avβ3/ PI3K/AKT/eNOS/ NO signaling (Y. Wang et al., 2011). OPN also activates Nrf2 signaling, resulting in enhanced heme oxygenase expression and cell migration in glioma cells (Lu et al., 2012). In HCC cells OPN promotes TGF-β1 mediated hepatic stellate cell activation (Xiao et al., 2012) and also upregulates CXCR4, SDF-1α, and MMP-2 expression through binding to integrin αvβ3 and CD44v6 (R. Zhang et al., 2011). Functionally, OPN is required for vascular mimicry in HCC cells (Liu et al., 2011).

Gimba and colleagues have reported that OPN-c promotes distinct aspects of prostate cancer progression (Tilli et al., 2012a). In human prostate cancer cell lines OPN is regulated by the activity of ALDH7A1 (van den Hoogen et al., 2011) and by Ets-related gene (ERG). Prostate cancer PC3 cells overexpressing OPN displayed an increase in the number of invadopodia and gelatinolytic activity providing evidence of a role for OPN in modifying structural components to facilitate tumor cells' invasion *via* integrin αvβ3 (Desai et al., 2008). Functionally OPN regulates prostate tumor growth by regulating the expression of COX-2 correlating with higher tumor load, increased tumor cell infiltration, nuclear polymorphism, and neovascularization in xenograft models (Jain et al., 2006). Down-regulation of OPN expression by RNAi led to S-phase arrest, apoptosis and a decline in the

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malignant phenotype in prostate cancer cells (Y. Zhang et al., 2011; Zheng et al., 2011). The DePinho lab carried out detailed comparative transcriptomic and canonical pathway analyses of normal prostate epithelium versus poorly progressive Ptennull prostate cancers to determine pathways activated in indolent tumors. This analysis revealed activation of the TGFβ/BMP-SMAD4 signaling axis with cyclin D1 and OPN as key mediators of prostate cancer growth and metastatic progression, which together with PTEN and SMAD4, form a four-gene signature that is prognostic of prostate-specific antigen (PSA) biochemical recurrence and lethal metastasis in human prostate cancer (Ding et al., 2011).

We found that the expression of OPN correlates with the aggressive phenotype of the breast cancer cells *i.e.* the expression of OPN is acquired as the breast cancer cells become more aggressive. Knocking down expression of endogenous OPN reduced invasive behavior and anchorage-independent growth and suppressed tumor take in immunocompromised mice indicating a role for OPN in influencing tumorigenicity (Shevde et al., 2006). In breast cancer, several independent studies have implicated OPN to impact signaling *via* hyaluronan synthase 2 (Cook et al., 2006), Wnt-β-catenin-Tcf-4 (T-cell factor4/ lymphoid enhancer factor1) signaling (Ravindranath et al., 2011), p70S6K/mTOR phosphorylation (Ahmed and Kundu, 2010), Src and Hsp90-dependent pathways (Mutrie et al., 2011). Human breast cancer cells overexpressing OPN show increased anchorage-independent growth in soft agar. These cells also showed increased lymphovascular invasion, lymph node metastases, and lung micrometastases, indicating that OPN is a key molecular player involved in lymphatic metastasis of breast cancer (Allan et al., 2006). OPN induces increased invasiveness and plasminogen activator expression of human mammary epithelial cells (Tuck et al., 1999) and also activates VEGF-dependent tumor progression and angiogenesis signaling cascades (Chakraborty et al., 2008b). OPN influences multiple signal transduction pathways through activation of EGF receptor (Tuck et al., 2003) (Zhang et al., 2003) (Das et al., 2004). OPN-initiated increases in migration, motility and invasion have been attributed to enhanced expression of the αvβ3 integrin, CD44 cell surface receptors, αvβ5 and β1-integrin expression, and increased Met kinase activity (Tuck et al., 2000; Furger et al., 2003; Khan et al., 2005). Studies from our laboratory showed that the expression of OPN and the tumor suppressor Merlin are inverse in breast cancer. The loss of Merlin is concomitant with a gain in OPN expression. We further demonstrated that OPN targets Merlin for AKT-mediated ubiquitin degradation in breast cancer. This provided the first evidence that OPN can cause degradation of a tumor suppressor protein (Morrow et al., 2011; Morrow and Shevde, 2012).

Osteolytic lesions are a painful consequence of metastasis of breast cancer cells to bone in an overwhelming majority of breast cancer patients. Findings from our group demonstrated for the first time that aberrant Hh signaling in metastatic breast cancer cells perturbs the dynamic equilibrium between the activities of bone-forming osteoblasts and bone-resorbing osteoclasts culminating in osteolysis. This is mediated, in part, by the upregulation of OPN, which in turn enhances osteoclast activity by up-regulating bone-resorbing proteases cathepsin K and MMP9. Thus, blocking aberrant Hh signaling is an approach to reduce OPN and consequently bone resorption in metastatic breast cancer (Das et al., 2009; Das et al., 2011; Harris et al., 2011; Das et al., 2012).

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OPN induction is required for tumor promoter-induced transformation of prenoplastic mouse cells (Chang et al., 2003) and facilitates dimethylbenz(a)anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA)-induced cutaneous carcinogenesis through prevention of apoptosis (Hsieh et al., 2006). OPN induced during transformation provides a microenvironment that facilitates tumorigenic transformation of pre-neoplastic JB6 cells by inhibiting anoikis through its RGD-dependent suppression of caspase-8 activity, which is mediated in part through the activation of FAK at Tyr^{861} (Y.H. Hsieh et al., 2013). In contrast, host-derived OPN suppression of extrinsic cutaneous squamous cell carcinoma (SCC) cell progression is likely mediated by elicitation of an early innate inflammatory response, through its function as a chemoattractant and/or by enhancing survival of inflammatory cells (Hsieh et al., 2012). OPN expression in melanoma specimens was found to be inverse that of a heat-shock protein, DNAJB6. By recruiting HSPA8 and protein phosphatase, PP2A, DNAJB6 caused dephosphorylation of glycogen synthase kinase 3β (GSK3β) leading to degradation of β-catenin, subsequent loss of TCF/LEF activity and decreased OPN expression (Mitra et al., 2012). Two independent studies have reported that OPN signaling activates nuclear factor-inducing kinase (NIK) and pp(60c-Src) kinase activity culminating in increased motility/migration and growth of melanoma cells (Rangaswami et al., 2004; Samanna et al., 2006).

OPN was highly expressed in metastatic hepatic lesions from colorectal cancer (CRC) compared to primary CRC tissue and adjacent normal mucosa. Exogenous expression of OPN in CRC cells increased heterotypic adhesion with endothelial cells (Huang et al., 2012). OPN induced by macrophages contributes to metachronous liver metastases in colorectal cancer (Imano et al., 2011). A recent study reports on the reciprocal interactions between TAM and CD44-positive CRC cancer cells *via* OPN/CD44. Macrophages, when co-injected or co-cultured with CD44-positive CRC cells, produced higher levels of OPN, which in turn facilitated the tumorigenicity and clonogenicity of the CRC cells (Rao et al., 2013).

5. OPN in clinical evaluations

OPN has been greatly advocated as a suitable biomarker as its secreted levels may be measured less invasively. Several reports point to the possibility of its use as marker with diagnostic or prognostic value.

There is a broad distribution of OPN in human carcinomas. When considering all sites, OPN expression significantly correlated with tumor stage (Coppola et al., 2004). OPN gene was one of the 5% most highly expressed genes in 20 out of 35 cancer microarray data sets in comparison with normal tissue in at least 30% of cancer patients (Atai et al., 2011). Meta-analysis of data from the published literature and from RNA microarrays deposited in Oncomine showed its association with 34 cancers and its overexpression in the metastases of colorectal cancers, lung cancers and melanomas, but not in ovarian cancer (Weber et al., 2011) (Fig. 2). One of the pioneering studies evaluating serial plasma levels of OPN was done by the Chambers lab. They conducted a prospective clinical study measuring serial OPN plasma levels by ELISA in 158 women with newly diagnosed metastatic breast cancer throughout the course of their disease. This study revealed that in women with metastatic

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breast cancer, increases in OPN levels over time were strongly associated with poor survival (Bramwell et al., 2006). In breast cancer, high expression of OPN was associated with frequent microcalcification deposition in the lesions and it is speculated that the expression of this glycoprotein by breast cancer cells plays a role in the preferred bone homing of breast metastases (Bellahcene and Castronovo, 1995). It was also seen that higher OPN levels in patients with metastatic breast cancer may be associated with an increased number of involved sites and decreased survival (Singhal et al., 1997; Tuck et al., 1998).

Chang et al. determined that OPN expression is associated with keratinocyte differentiation and that it is expressed in premalignant solar/actinic keratosis and in malignant skin lesions such as SCC, which have metastatic potential, but is minimally expressed in solid basal cell carcinomas (Chang et al., 2008). OPN is also a promising prognostic biomarker in NSCLC. High expression of OPN in these tumors was associated with poor patient outcome and it was a strong, independent prognostic factor for both relapse free and overall survival (Rud et al., 2013). OPN plasma levels in the patients with NSCLC are significantly elevated as compared to those in the controls (Han et al., 2013). In adult soft tissue sarcomas, OPN may have potential as a prognostic marker (Bramwell et al., 2005). Increased plasma OPN expression was noted in CRC patients (Fan et al., 2013) together with polymorphism in the rs9138 (+1239; 3′UTR: 3′untranslated regions) and rs1126616 (+750; exon 7) regions of *SPP1* promoter that were associated with CRC risk. In CRC an additive effect was observed for biomarker panels with carcinoembryonic antigen (CEA), Transferrin Receptor-1 (TFRC), Macrophage migration inhibitory factor (MIF), OPN and cancer antigen 242 (CA242). This biomarker panel identified CRC patients with a sensitivity of 56% indicating that this combination of proteins may be a suitable serological biomarker for detection of CRC (Thorsen et al., 2013). Elevated content of OPN in plasma and tumor tissues of patients with laryngeal and hypopharyngeal carcinoma is associated with metastasis and prognosis (Li et al., 2012). Mass spectrometry profiling of highly fractionated plasma from cirrhosis and HCC patients identified OPN as significantly up-regulated in HCC cases, compared to cirrhosis controls. OPN was more sensitive than alpha-fetoprotein for the diagnosis of HCC. In addition, OPN performance remained intact in samples collected 1 year before diagnosis (Shang et al., 2012). Monitoring increased levels of postoperative serum OPN has also been proposed for assessing treatment response and tumor recurrence after resection of hepatitis B-related HCC (Zhou et al., 2013). In HCC tissues, OPN levels are found to be significantly higher in recurrent tumor tissues compared to non-recurrent tissues. Also patients with higher OPN levels had significantly shorter median survival time and recurrence time compared to the ones with lower OPN levels. It was also observed that co-index of OPN/ Bcl-2 levels was an independent prognostic factor for both overall survival and time to recurrence in this cancer type (Deng et al., 2013).

OPN is a marker of osteoclastic activity in multiple myeloma patients, as well as a regulator of angiogenesis. Sfiridaki et al. measured serum OPN levels in untreated multiple myeloma patients and examined the relation to markers of osteolytic and angiogenic activity. Serum OPN levels were significantly higher in patients with advanced stage or grade of myeloma disease. Serum OPN levels significantly decreased after treatment and there was a positive correlation of OPN with the bone turnover marker N-terminal propeptide of procollagen type I (NTx) and the angiogenic markers VEGF and bone marrow microvessel density

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supporting OPN as a dual marker of bone destruction and angiogenic activity in myeloma patients (Sfiridaki et al., 2011).

Increased OPN expression has also been observed correlating with various degrees of severity in Helicobacter pylori infection (Chang et al., 2011), laryngeal and hypopharyngeal primary and metastatic carcinomas (Lu et al., 2011), papillary thyroid carcinoma accompanied by microcalcification and lymph node metastasis (Sun et al., 2011) but not in Head and Neck Squamous cell carcinoma (HNSCC) (Lim et al., 2012). A contrasting study reported a prognostic value of OPN in patients treated with primary radiotherapy for HNSCC. OPN levels increased in patients with local recurrence who were treated with primary radiotherapy for locally advanced HNSCC (Etiz et al., 2013). Changes in levels of OPN are involved in ovarian clear cell carcinoma cell invasion and it could have a crucial role in ovarian clear cell carcinoma therapy (Matsuura et al., 2010). The diagnostic utility of OPN is similar to that of ultrasonographic evaluation and CA-125 level assessment especially for differential diagnosis of endometriotic cysts (Moszynski et al., 2013). Studies of melanoma patients showed that there was a trend for increased risk of death with increasing OPN levels. Individuals with untreated stage IV disease had higher median OPN levels compared to those with treated stage I–III disease (Filia et al., 2013). In nasopharyngeal carcinoma (NPC) OPN mRNA and protein overexpression was strongly related to T stage, N stage and clinical stages of NPC, suggesting that OPN may be involved in NPC metastasis and progression (H.H. Wang et al., 2011). In patients with malignant pleural mesothelioma (MPM) baseline OPN levels were an independent negative predictor of survival (Hollevoet et al., 2011). Combined measurements of plasma OPN and serum soluble mesothelin-related peptides appear to improve sensitivity and specificity in terms of combined risk index (Cristaudo et al., 2011). High cerebrospinal fluid OPN levels in childhood acute leukemia patients may be used as evidence for CNS involvement (Incesoy-Ozdemir et al., 2013). OPN has also been shown to be an important player in the occurrence and metastasis of lung cancer (Wang et al., 2013). The serum levels of both OPN and tissue inhibitor of metalloproteinase 1 (TIMP-1) can clearly distinguish pancreatic ductal adenocarcinoma from chronic pancreatitis and healthy control subjects. Also, high serum levels of OPN were significantly correlated with reduced patient survival for pancreatic cancer (Poruk et al., 2013). OPN expression is activated in vestibular schwannomas, most of which arise due to the functional loss of Merlin protein. OPN mediates Merlin protein degradation (Morrow and Shevde, 2012); thus OPN may also exert a pivotal role in Merlin depletion in schwannomas (Torres-Martin et al., 2013). A study of 225 bladder urothelial carcinoma (BUC) patients compared to age/sex-matched healthy volunteers revealed that the mean plasma OPN levels were significantly higher in BUC patients than in controls, significantly higher in patients with high-grade BUC than in those with low-grade BUC, and significantly higher in patients with muscle-invasive BUC than in those with non-muscle-invasive BUC. The metastatic BUC had the highest OPN expression. Also, higher plasma OPN level was associated with a lower overall survival (Zhao et al., 2012). Prostate cancer studies have shown that plasma OPN is as good as PSA at predicting treatment response after chemotherapy however not useful as a biomarker of increasing tumor burden within localized prostate cancer. OPN neither distinguished high-risk prostate cancer from other localized prostate cancer nor correlated with serum PSA at baseline (Thoms et al., 2012).

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Clear cell renal cell carcinoma (CCRCC) studies reveal that expression of EGFR was inversely associated with OPN levels and NF-κB activation (Matusan-Ilijas et al., 2013).

OPN spliced variants possibly have their unique place as cancer markers. Compared with the normal breast tissues, the expression of OPN-c was found to be negatively associated with the E-cadherin and β-catenin levels. Several studies are strongly indicative of potential of OPN-c as a biomarker. OPN-b is increased in lung cancers and pancreatic cancers. OPN-c is increased in gynecologic as well as pancreatic cancers. Elevation in OPN-c of 2 standard deviations above the normal mean value also detected a fraction of breast cancers and lung cancers. Specifically, breast carcinomas were associated with significantly higher levels of OPN-c mRNA in the blood than carcinomas *in situ*. In lung cancer patients, the OPN-c blood RNA levels had an increasing trend with tumor grade (Hartung and Weber, 2013). OPN-c was also specifically expressed in ovarian tumor samples and demonstrated to prompt PI3K/Akt signaling (Tilli et al., 2011). The RNA message for OPN-c was present in 16 of 20 breast cancers (80%), but was undetectable in 22 normal specimens obtained from reduction mammoplasty. In a total of 178 breast specimens analyzed, OPN-c was present in 78% of cancers, 36% of surrounding tissues and 0% of normal tissues. Furthermore, OPN-c detects a higher fraction of breast cancers than estrogen receptor (ER), progesterone receptor or HER2. In conjunction, OPN-c, ER and HER2 reliably predict grade 2–3 breast cancer (Mirza et al., 2008). The expression of OPN-c correlated with lymph node metastasis and advanced TNM stage and histologic grade. Elevated expression of OPN-c also correlated with tumor recurrence or metastasis as well as triple negative breast cancer subtype. Overall, the expression of OPN-c was an independent prognostic factor for both disease-free and overall survival of breast cancer patients (Pang et al., 2013). OPN-b is the dominant kind of OPN isoform in gastric cancer (GC) cell lines. Although the expression levels of three variants were all elevated in GC tissues, increased OPN-b or OPN-c expression could correlate with clinicopathological features. Functionally OPN-b most strongly promoted GC cell survival while OPN-c most effectively stimulated GC metastatic activity (Tang et al., 2013).

Certainly it appears that OPN expression has significant correlative relationship with aggressive disease and poor prognosis. However, OPN is not a universal marker for tumors and metastasis. It is upregulated in response to stress and inflammation and hence its use is clinically not favored. Additionally, there are exceptions to note, such as HCC which did not show a diagnostic role of plasma OPN as an adjuvant or alternative marker to established markers (Khalil et al., 2013). MPM patient studies showed lack of association between exposure duration or benign asbestos-related disease and OPN levels (Felten et al., 2013). For MPM plasma OPN had a superior diagnostic accuracy to serum but there was no specific advantage over serum mesothelin (Creaney et al., 2011). Surprisingly, OPN expression in PDAC may have a protective effect independent of tumor stage. The median and 2 year overall survival was longer when OPN was expressed in PDAC. The expression was observed predominantly in the cytoplasm of the tumor cells (Collins et al., 2012).

In addition to expression and spliced variants, OPN nucleotide polymorphism may also have potential as disease marker. OPN variant at nt −443 (CC) was significantly different between stage IV lung cancer patients compared with all other stages. Also these patients had

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significantly higher incidence of bone metastasis. The survival rates for patients with the C/C genotype were significantly lower than for patients with the other two genotypes (C/T, T/T). Thus OPN −443C/T polymorphism is a potential predictive marker of survival in lung cancer patients and it is correlated with bone metastasis significantly (Chen et al., 2013). In papillary thyroid cancer patients OPN protein was not expressed in normal thyroid tissues while tumor samples showed to have high expressions of OPN and these were more prevalent in −443CC carriers than TT carriers. The CC carriers and OPN expression were closely associated with the cervical lymph node metastasis and angiolymphatic invasion (Mu et al., 2013). OPN promoter polymorphisms are associated with susceptibility to gastric cancer. The combination of SNP −443 (T/C or C/C) and −616 (T/T or T/G) significantly increases susceptibility to gastric cancer (Lee et al., 2013).

6. Approaches to inhibit OPN expression and/or function

Given its potent role in promoting tumorigenicity and metastasis, several avenues have been explored to intervene in the downstream events mediated by OPN. One of the most explored approaches is the use of dietary constituents. Two independent studies have investigated the effect of resveratrol (trans-3,4′,5-trihydroxystilbene) since it is reported to display antitumor activities on a variety of human cancer cells. While resveratrol did not have a direct effect on myeloma cells, it promoted dose-dependent expression of osteoblast markers like osteocalcin and OPN in human bone marrow mesenchymal stem cells and stimulated their response to 1,25(OH)2 vitamin D3, making a case for resveratrol in treating multiple myeloma or its complications (Boissy et al., 2005). In a complementary study, Hong et al. showed that the anti-nephrolithic activity of resveratrol is mediated in part, due to its ability to inhibit OPN (Hong et al., 2013). In a TRAnsgenic Mouse Prostate adenocarcinoma (TRAMP) model, administration of the soy isoflavone genistein improved survival and reduced the mean weight of prostates with poorly differentiated cancer concomitant with significant inhibitory effect on OPN transcript levels in prostates displaying advanced prostate cancer consistent with the possibility that dietary genistein may delay the progression from benign to malignant tumors by inhibiting OPN expression (Mentor-Marcel et al., 2005). A study by Lv et al. reported the combined benefit of treating SKOV3 ovarian cancer cells with curcumin (diferuloylmethane) and a polysaccharide extract obtained from Ocimum basilicum (basil polysaccharide) with a reduction on OPN transcript and protein levels and decreased invasive phenotype of the tumor cells (Lv et al., 2013). In an independent evaluation, Chakraborty et al. demonstrated that curcumin abrogated OPN-induced VEGF expression and curbed OPN-induced VEGF-dependent breast tumor angiogenesis *in vivo* (Chakraborty et al., 2008a). In human oral cancer CAL-27 cells the chemopreventive effect of the aqueous garlic extract S-allylcysteine (SAC) reduced OPN levels *in vitro* (Pai et al., 2012). In HCC daily administration of thalidomide reduced the OPN content of the liver tumors (detected using immunohistochemistry). There were significant differences in the OPN levels of the tumors among the early intervention, late intervention and negative control groups supporting the contention that thalidomide may inhibit the generation of OPN and thereby inhibit the infiltration and metastasis of tumors (Lin et al., 2013). Andrographolide a natural diterpenoid lactone isolated from Andrographis paniculata has been shown to possess inhibitory effect on cancer cell growth. In a study by

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Kumar et al., Andrographolide was shown to inhibit breast cancer cell proliferation, migration and arrest cell cycle at G2/M phase and induce apoptosis through a caspase independent pathway. Andrographolide inhibited expression of OPN and VEGF simultaneous with decreased breast tumor growth in orthotopic NOD/SCID mice model (Kumar et al., 2012).

Proteolytic cleavage of OPN by thrombin has been reported to increase its biologic activity. Inhibition of thrombin with the thrombin-specific inhibitor Argatroban resulted in notable decreased cell growth, colony-forming ability, adhesion, and migration of MDA-MB-468-OPN expressing breast cancer cells relative to untreated controls. Moreover, following mammary fat pad injection, treatment with Argatroban (9 mg/kg/day) significantly increased the *in vivo* tumor latency and reduced primary tumor growth of 468-OPN cells. Furthermore, Argatroban treatment caused a significant decrease in lymphatic metastasis relative to untreated controls suggesting that thrombin inhibitors such as Argatroban may hold potential as therapeutic agents to combat breast cancer progression (Schulze et al., 2008).

Minaj-Tehrani et al. used a novel approach to create a triple mutant of OPN, which is mutated at three O-glycosylation sites, on lung cancer development in K-ras (LA1) mice, a murine model for human non-small cell lung cancer. Aerosolized lentivirus-based OPN triple mutant delivered into the lungs of K-ras (LA1) mice inhibited lung tumorigenesis. In addition, the OPN-mediated Akt signaling pathway was inhibited. OPN triple mutant also decreased NF-κB activity and the phosphorylation of 4E-BP1, while facilitating apoptosis in the lungs (Minai-Tehrani et al., 2013a).

OPN-induced signal transduction involves activation of both Src and Hsp90-dependent pathways. Src kinase and Hsp90 play important roles in malignancy-promoting signaling pathways in many cancers; their targeting agents are presently in clinical trials. Mutrie et al. devised a clever strategy to use OPN to make tumor cells more vulnerable to these classes of inhibitors. They determined that OPN expression or treatment enhanced sensitivity to two specific inhibitors, an Hsp90 inhibitor and a Src kinase inhibitor. In contrast, decreasing OPN levels *via* shRNA knockdown decreased inhibitor effects. Thus, OPN could potentially be useful clinically as a predictive marker in identifying patients who may benefit from either Hsp90 or Src kinase inhibitor therapy (Mutrie et al., 2011). The approach of inhibiting endogenous OPN has been tested in the laboratory and animal setting using multiple approaches. This includes the use of anti-sense oligonucleotides (Shevde et al., 2006), aptamers (Talbot et al., 2011) and shRNA (Shevde et al., 2006; Pang et al., 2011). In each of the studies, abrogating the expression of OPN resulted in decreased proliferation and/or survival, malignant and/or metastatic potential. In NSCLC, the use of a monoclonal antibody AOM1 identified using phage display technology was shown to be effective in significantly inhibiting growth of large metastatic tumors in the lung when used as a single agent or in combination with Carboplatin (Shojaei et al., 2012).

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7. Conclusion

OPN is a complex molecule, in terms of its multidimensional role, especially from the perspective of host-derived and tumor-derived OPN. As summarized above, the vast majority of the studies appear to converge on the fact that increased levels of circulating OPN and/or increased OPN expression by the tumor cells correlate with an unfavorable prognosis. Further efforts are needed to understand the source of increased OPN in circulation *i.e.* is that OPN being produced by host inflammatory cells in response to a growing tumor or whether it is originating from the tumor cells. Investigations on the isoforms of OPN in cancer seem to indicate a compelling role for the OPN-c isoform. Active research is also underway to characterize approaches to effectively reduce the overall OPN levels. While it may be too early to comment, efforts in the direction of using dietary compounds may be beneficial due to their minimal toxicity to non-cancerous tissues. The development of small molecule inhibitors to decrease OPN production by the tumor cells or to counter the signaling cascades elicited by OPN seems to be promising also from the possibility of enhancing sensitivity to chemotherapeutics.

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Abbreviations

BPH	benign prostatic hyperplasia
BRMS1	breast cancer metastasis suppressor 1
COX-2	cyclooxygenase-2
CRC	colorectal cancer
EMT	epithelial-to-mesenchymal transition
GVHD	graft-versus-host disease
HCC	hepatocellular carcinoma
MMP	matrix metalloproteases
NPC	nasopharyngeal cancer
NSCLC	non-small cell lung carcinoma
OPN	osteopontin
PDAC	pancreatic ductal adenocarcinoma
PGE_2	prostaglandin E_2
SPP1	secreted phosphoprotein 1
Tcf-4	T cell factor1/lymphoid enhancer factor1

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TGF-β	transforming growth factor-β
uPA	urokinase plasminogen activator
VEGF	vascular endothelial growth factor

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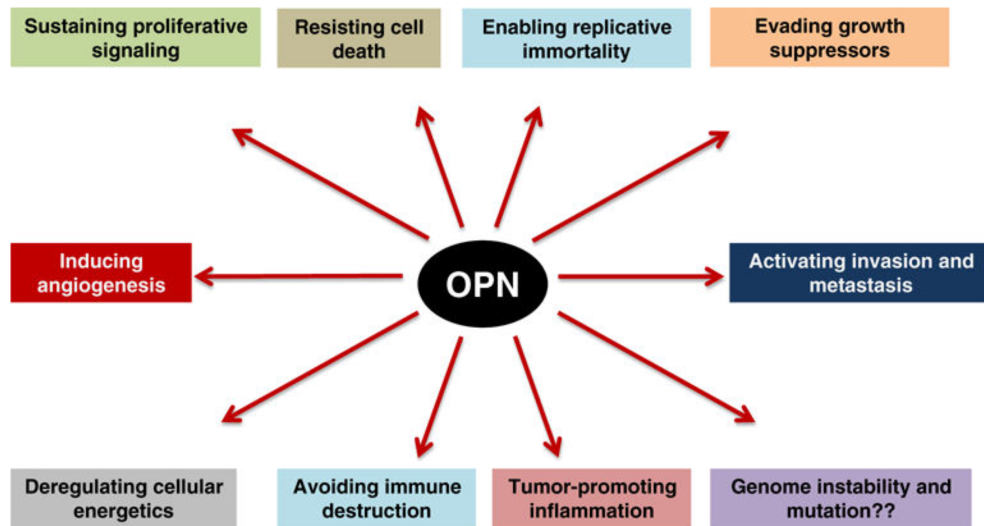

Fig. 1.
OPN influences all the six hallmarks of cancer and also three of the enabling characteristics of cancer. As of this time there is no data to clearly implicate a role for OPN in genomic instability and mutation.

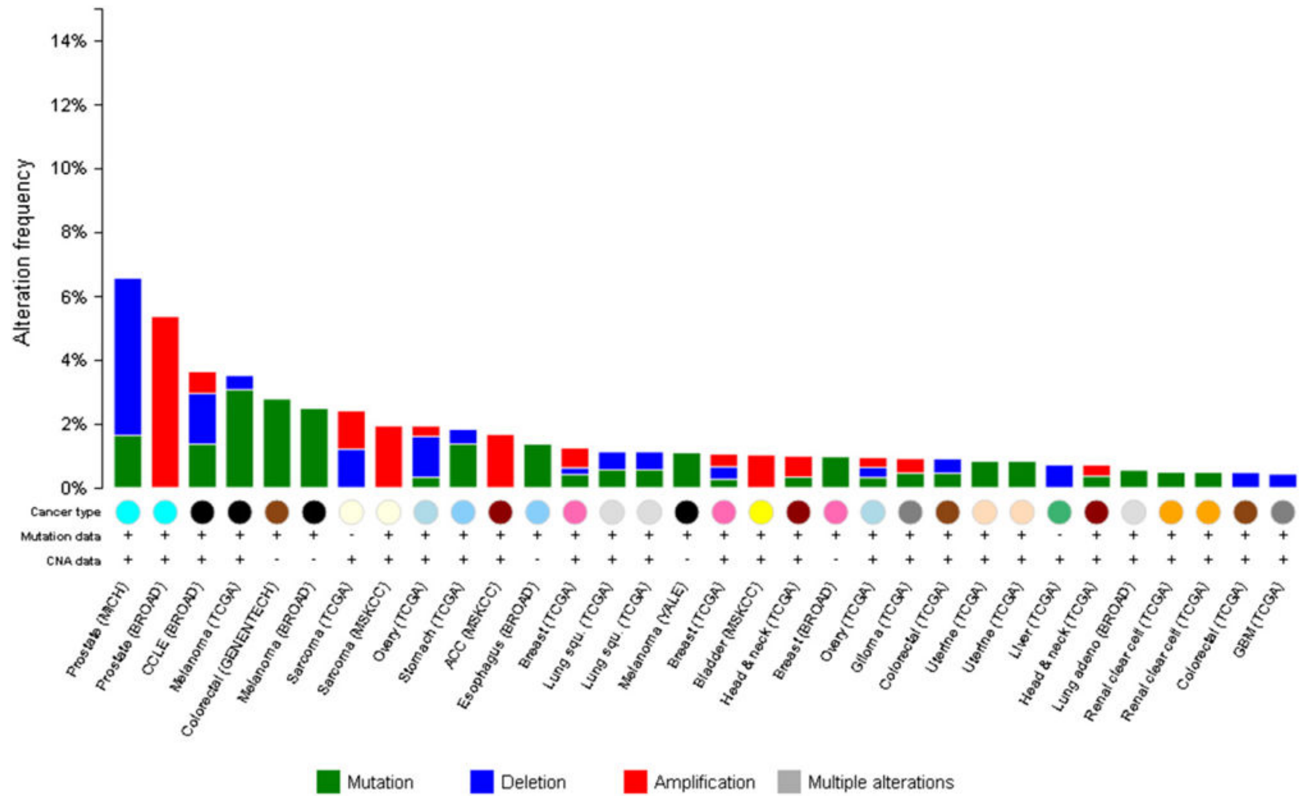

Fig. 2.

Cross-cancer alteration for SPP1 (52 studies/1 gene). The data depicts the frequency of alteration in SPP1 across several cancer types. This data was obtained by querying the CBio Database for the transcript and mutation data for SPP1, the gene for OPN protein. This data queries 52 independent studies that are deposited at CBio Cancer Genomics Portal (Cerami et al., 2012).

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