Role of osteopontin in cancer: From pathogenesis to therapeutics (Review)

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Abstract. Osteopontin (OPN) is an extracellular matrix protein secreted by various types of cells, and serves multiple physiological roles such as modulating bone cell maturation, immune responses, tissue repair and regeneration. Aberrant OPN expression contributes to tumor genesis and development. This indicates that OPN serves a crucial role in tumor genesis and could serve as a potential target for tumor interventions. The present review firstly introduces the molecular structure, receptors and physiological functions of OPN. Subsequently, the present review elaborately addresses the pivotal role served by OPN, and its mechanism in tumor initiation and progression, metastasis, and drug resistance. Furthermore, the present review summarizes currently reported OPN-based tumor intervention strategies. Lastly, the present review also provides perspectives on how to deepen the insights into the exact role of OPN in tumorigenesis, with the aim of aiding the development of novel strategies for tumor therapeutics. The present review broadens the knowledge regarding the pathophysiological role of OPN, so that novel OPN-based cancer treatment strategies may be proposed.

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Contents

1. Introduction

Cancer is a disease that poses threats to human health and life, and is characterized by aberrant cellular proliferation and the development of malignant tumors. According to data provided by the World Health Organization, millions of individuals worldwide are diagnosed with cancer annually (1,2). The incidence and mortality rates have exhibited an upward trend, and are subject to temporal and regional variations (3). Although advancements in oncology research have been made by scientists and clinicians in areas such as drug discovery, immunotherapy and radiotherapy, effective treatment of cancer is still facing great challenges, such as drug resistance, immune tolerance and severe side-effects (4-6). It is imperative to unravel the mechanisms underlying tumorigenesis and to develop novel intervention strategies.

Osteopontin (OPN) is a multifunctional glycophosphoprotein encoded by the secretory phosphoprotein 1 (SPP1) gene, which is expressed in various types of cells and tissues, including in the bone, dentin, cementum, hypertrophic cartilage, kidney, brain, bone-marrow-derived metrial gland cells, vascular tissues, cytotrophoblasts of the chorionic villus in the uterus and decidua, ganglia of the inner ear, brain cells, specialized epithelia found in mammary, salivary and sweat glands, bile and pancreatic ducts, distal renal tubules and the gut, as well as in activated macrophages and lymphocytes (7,8). OPN was first reported as a marker of transformation of epithelial cells in 1979 (9). Subsequently, more variants of OPN and their corresponding functions have been identified. For example, OPN splicing isoforms in solid tumors have been investigated in breast cancer, mesothelioma and lung cancer (10,11). As a

secreted protein, OPN binds with its receptors, such as integrin or CD44, to exert functions, including modulating cell proliferation, adhesion, inflammatory responses, osteogenesis and wound healing (8). The role of OPN in tumorigenesis and development has attracted increasing attention (12,13). Abnormal OPN expression has been observed in different types of cancer such as brain, lung, kidney, liver, bladder and breast cancer (13,14). Diverse hypotheses have been proposed regarding the association between OPN and tumorigenesis; however, to the best of our knowledge, its precise molecular mechanisms remain to be illustrated. Given the pivotal role of OPN in tumorigenesis and progression, OPN-based interventions have been developed and applied in both basic research and clinical settings (15-17).

The present review, after briefly introducing the molecular structure, receptors and physiological functions of OPN, describes how OPN participates in cancer initiation, progression, metastasis and drug resistance. Furthermore, the present review summarizes current OPN-based tumor intervention strategies. The present review also provides perspectives on how to deepen the insights regarding the exact role of OPN in tumorigenesis in order to help develop novel strategies for tumor therapeutics. The present review broadens the knowledge regarding the pathophysiological role of OPN, so that novel OPN-based cancer treatment strategies may be proposed.

2. Profile of OPN

OPN was first reported as a transformation marker of malignant cells by Senger *et al* (9) in 1979. With the deepening of research, more definitions of OPN have been determined, including bone sialoprotein, SPP1 and early T-lymphocyte activation 1 (Eta-1) (8). Based on mRNA transcript variants, OPN can be translated into five subtypes, including OPN-a, OPN-b, OPN-c, OPN4 and OPN5, which can exist in secretory or intracellular forms (10). Therefore, OPN has multiple functions in pathophysiological conditions such as inflammation, cell survival, adhesion, migration, differentiation, apoptosis and bone matrix mineralization (18,19). Comprehensive understanding of the protein structure, receptors and functions of OPN is necessary and crucial in order to further reveal its mechanism involved in tumor genesis and development, and to develop therapeutic strategies.

Genomic location and structure of OPN. OPN is encoded by the SPP1 gene located on chromosome 4q22.1 (19). The SPP1 gene contains seven exons, which undergo selective splicing to generate distinct variants. At present, seven exons of SPP1 have been reported. Exon 1 remains untranslated, whereas exons 2-7 contain coding sequences. Exon 2 encodes a signal peptide along with two amino acids constituting the mature protein; exon 3 encodes a serine phosphorylation motif; exon 4 encodes a proline-rich region and transglutaminase site; and exon 5 encodes an additional protein phosphorylation site. Notably, exons 6 and 7 account for >80% of the expressed OPN protein (19). Five isoforms of OPN have been reported, including OPN-a (comprising all exons and consisting of 314 amino acids), OPN-b (lacking exon 5 and comprising 300 amino acids), OPN-c (lacking exon 4 and comprising 287 amino acids), OPN4 (lacking exons 4 and 5, and consisting of 273 amino acids) and OPN5 (containing an additional exon, with a length of 327 amino acids) (10,20). Distinct splicing of the SPP1 gene has been implicated in cancer occurrence, progression and prognosis (19).

Protein structure of OPN. Human OPN contains ~314 amino acid residues, with a molecular weight ranging between 41 and 75 kDa, depending on different post-translational modifications (8,21). OPN contains several highly conserved domains, including the aspartate domain, arginine-glycine-aspartic acid (RGD) domain, serine-valine-valine-tyrosine-glutamate-leucine-arginine (SVVYGLR) domain, thrombin cleavage domain, calcium-binding domain and C-terminal heparin-binding domain (22). Given that OPN is a secreted protein, it is present not only in various tissues but also in biological fluids. The secreted OPN is subjected to various post-translational modifications, including glycosylation, phosphorylation and sulfuration, which endows OPN with diversified biological functions (8). Fig. 1 schematically illustrates the structure and domains of OPN.

Receptors of OPN. OPN needs to bind with its receptors to exert its function. The well-characterized receptors of OPN include integrins and CD44 (23,24). Notably, under some conditions, OPN is subjected to protease cleavage to expose its specific domains, which exhibit binding affinity for potential receptors (25).

Integrins are transmembrane heterodimers that recognize various ligands, including OPN and other extracellular matrix proteins and cell surface proteins (26). The RGD sequence of OPN exhibits a strong binding affinity for integrins, including $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 8\beta 1$, $\alpha 5\beta 1$ and $\alpha_{IIb}\beta 3$ (27,28). Another integrin-binding domain (SVVYGLR) can only be exposed after thrombin cleavage at Arg^{168}-Ser^{169} (29). The exposed SVVYGLR interacts with integrin subtypes such as $\alpha 9\beta 1$, $\alpha 4\beta 1$ and $\alpha 4\beta 7$ (25,28,30). Similarly, plasma proteases cleave OPN at Lys^{154}-Ser^{155}, producing an N-terminal OPN fragment that binds more strongly to $\alpha 5\beta 1$ and $\alpha v\beta 3$ integrins than the full-length OPN (25). MMP could cleave OPN at various sites such as Gly^{166}-Leu^{167}, Ala^{201}-Tyr^{202} and Asp^{210}-Leu^{211}, producing a fragment that preferably binds with the $\alpha 4\beta 1$ isoform of integrin (29).

CD44, also known as hyaluronic acid receptor, is expressed in various cell types such as osteocytes, endothelial cells, fibroblasts, epithelial cells and smooth muscle cells (31). The C-terminal fragment heparin-binding site of OPN can directly interact with CD44 variants CD44v3 and CD44v6 (30).

Therefore, OPN, with or without cleavage, interacts with integrins or CD44 to regulate multiple cellular processes, including cell attachment, migration, chemotaxis and immune modulation in diverse types of cells (24).

Pathophysiological role of OPN. OPN is expressed in various types of cells and tissues. With the deepening of research, diverse functions of OPN in both physiological and pathological conditions have been revealed (32,33).

Orchestrating the immune response. OPN is also known as Eta-1 and can trigger the immune response of macrophages, T cells and B cells (34). For example, OPN binds with

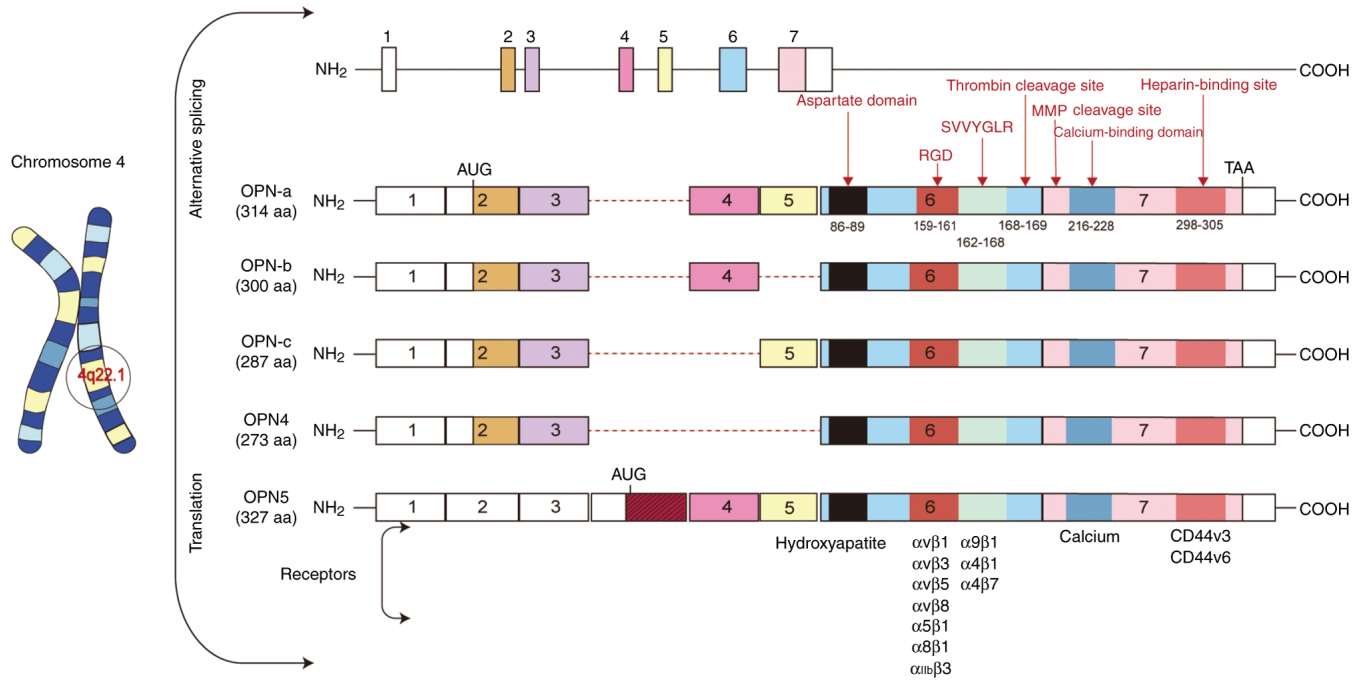

Figure 1. Schematic representation of the protein structure of OPN. Full-length OPN-a derived from the SPP1 gene contains seven exons, while other variants of OPN derived from the SPP1 gene lack distinct exons. OPN-b derived from the SPP1 gene lacks exon 5; OPN-c derived from the SPP1 gene lacks exon 4; OPN4 derived from the SPP1 gene lacks exons 4 and 5; and OPN5 derived from the SPP1 gene with one extra exon between exons 3 and 4. COOH, carboxyl group; NH_2, amino group; OPN, osteopontin; RGD, arginine-glycine-aspartic acid; SPP1, secretory phosphoprotein 1; SVVYGLR, serine-valine-valinetyrosine-glutamate-leucine-arginine.

integrin (αvβ3) of macrophages and reduces the production of anti-inflammatory IL-10, while its binding with CD44 promotes the secretion of proinflammatory IL-12 (23). OPN also influences the migration of immune cells (27,35). Wang and Denhardt (27) reported that OPN served as a type 1 T helper cell cytokine, contributing to mucosal defense against viral pathogens. OPN may regulate inflammatory reactions by stimulating the natural immune response of macrophages and neutrophils (27). OPN could also be secreted by activated T cells to aid in the recruitment and migration of immune cells, particularly macrophages, toward the site of inflammation, resulting in persistence and exacerbation of the inflammatory response (36).

OPN exerts pro-inflammatory effects by activating inflammatory signaling pathways, such as the NF-κB and STAT3 pathways, which leads to the secretion of cytokines, including TNF-α and CD16 (37). Additionally, OPN modulates immune cell functions by enhancing macrophage chemotaxis and phagocytic activity, promoting their polarization toward the pro-inflammatory M1 phenotype, and activating the immune responses of T cells, natural killer cells and dendritic cells (38,39). Furthermore, OPN stimulates tumor cells to secrete IL-17, thereby activating the JNK/c-Jun signaling pathway and contributing to immunosuppressive effects (40). OPN also serves a critical role in mediating immune escape mechanisms, such as enabling tumor cells to evade immune surveillance through the suppression of T cell activity (41). Development of single-cell RNA sequencing (scRNA-seq) has provided a better way to define the context-dependent functions of OPN. Ding *et al* (42) utilized scRNA-seq and revealed that $CD163^+$ macrophages were enriched in lung tissues of patients with coronavirus disease 2019, and these cells highly expressed OPN. Wang *et al* (43) used scRNA-seq analysis and revealed that OPN expression was upregulated in menstrual blood cells from patients with endometriosis, which in synergy with inflammatory factors, such as IL-10 and IL-6, promoted local fibrotic processes.

Aberrant OPN expression may induce dysregulation of the immune response, thereby impairing the normal recognition and response to self-antigens and foreign antigens, which contributes to the initiation and progression of autoimmune disorders (44). Improper expression of OPN is associated with the pathogenesis of various autoimmune diseases (such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis and atherosclerosis) and other inflammatory diseases (including cardiovascular diseases, chronic obstructive pulmonary disease, inflammatory bowel disease, liver diseases and asthma) (27).

Regulating osteogenesis. OPN also participates in osteogenesis, regulating bone cell adhesion and osteoclast function, and promoting matrix mineralization. The strong affinity of OPN for hydroxyapatite leads to its accumulation in the bone (45-47). OPN exerts an effect on skeletal cell proliferation, differentiation and migration, while facilitating calcium phosphate mineralization (48). Given its crucial role in bone metabolism, aberrant OPN expression is associated with various types of bone diseases. In patient with osteolysis, OPN expression is downregulated, whereas in patients with fractures, OPN expression is increased (49).

Tissue repair. OPN exhibits an important role in tissue repair and regeneration by facilitating cell migration, proliferation, neoangiogenesis and the formation of fibrous connective

tissue (50). For example, OPN has been found to promote fibroblast proliferation during wound healing (50). Furthermore, Wen *et al* (51) found that, in a model of regenerating liver after partial hepatectomy, OPN promoted the inflammatory response and activated the IL-6/STAT3 pathway to facilitate the proliferation of hepatocytes and the repair of the liver. A previous study has demonstrated that OPN expression could induce vascular intimal thickening and promote neointimal formation following injury, suggesting a role in vascular remodeling (52). Upregulation of OPN leads to tissue fibrosis, including liver and kidney fibrosis, by facilitating the synthesis and deposition of extracellular matrix proteins (53).

Cardiovascular diseases. OPN also participates in the regulation of cardiovascular function. OPN is upregulated in atherosclerosis and present in atherosclerotic plaques, suggesting its potential relevance (54). Furthermore, it has been demonstrated that OPN induces vascular calcification by facilitating mineral uptake and formation of apatite crystals (55). Speer *et al* (56) further revealed that phosphorylation of OPN could induce vascular calcification.

In summary, OPN serves diverse and important pathophysiological roles in a context-dependent manner. Elucidating the intricate structure and multifaceted functionality of OPN will consequently facilitate the development of OPN-based diagnostic and therapeutic strategies.

3. Molecular mechanisms of OPN involved in tumor genesis and development

The role and mechanisms of OPN in tumor genesis and development have attracted increased attention (57-60). Increased OPN expression is observed in various malignancies, including breast cancer, leukemia, hepatocellular carcinoma (HCC), bladder cancer, colorectal cancer, melanoma, lung cancer, squamous cell carcinoma of the head and neck, and glioblastoma multiforme (13,61). Numerous studies have demonstrated that the upregulation of OPN is involved in tumorigenesis, chemotherapy resistance, angiogenesis and immunosuppression, and revealing how OPN participates in these processes is essential (62-67).

OPN is involved in cancer pathogenesis. One study has revealed high OPN expression in various types of cancer such as brain tumors, lung cancer, kidney cancer, liver cancer, bladder cancer, breast cancer, esophageal cancer, pancreatic cancer, gastric cancer, colorectal cancer and prostate cancer (13). The precise role and mechanism of OPN in cancer pathogenesis are not fully understood; however, the following aspects have been widely implicated in these.

Promoting cell survival and inhibiting apoptosis. Tumor cells exhibit anti-apoptosis capacities (68). Sun *et al* (69) demonstrated that OPN regulated Bcl-2 and Bax expression, thus enhancing the viability of tumor cells. Another group found that OPN could induce Bcl-2 expression and attenuate apoptosis (70). In addition, OPN facilitates tumor progression by regulating tumor surveillance mechanisms and inhibiting tumor cell apoptosis (71). Upregulated OPN interacts with integrin αvβ3 or CD44, facilitating complement factor H cell surface translocalization, and thus, complement-mediated cell death is suppressed (72). Zhou *et al* (73) found that OPN knockdown enhanced apoptosis and caused cell cycle arrest in leukemia stem cells.

Promoting cell migration and invasion. Tumor metastasis is closely associated with the capacity of cell migration and invasion (72,74). Irby *et al* (75) reported that overexpressed OPN in SW480, HT29 and HCT116 cells bound with its receptors, including integrins (αvβ1, αvβ3 and αvβ5) and CD44, and enhanced colon cancer invasion. OPN has the ability to mediate the adhesion and interaction between tumor cells and the surrounding matrix, thereby augmenting the metastatic potential of tumor cells (76). Kale *et al* (77) found that OPN, after binding with integrin (α9β1), triggered cyclooxygenase-2 (COX-2) and prostaglandin E2 expression, and thus, promoted tumor growth and metastasis. OPN induces the expression and activation of MMP-2, MMP-3 and urokinase-type plasminogen activator in an integrin-dependent manner, which promotes extracellular matrix degradation and consequent metastasis (78). The capacity of OPN to induce cellular migration and extracellular matrix degradation contributes to the invasive and metastatic potential of cancer (78).

Promoting angiogenesis. Angiogenesis is a feature of tumors, particularly solid tumors. Neovascularization enhances the supply of nutrients and oxygen, thus promoting tumor growth and metastasis (71,79). OPN is involved in tumor angiogenesis by facilitating the migration and proliferation of vascular endothelial cells, which promotes neovascularization (79). Gupta *et al* (80) reported that OPN activated MMP-9, which resulted in increased VEGF secretion and promoted the angiogenesis of prostate cancer, while OPN knockdown or αvβ3 mutation reversed these effects. Fukusada *et al* (81) reported that OPN induced VEGF expression and angiogenesis, which promoted pancreatic ductal adenocarcinoma progression.

Modulating the tumor microenvironment (TME). Tumor cells are surrounded by the TME, which consists of extracellular matrix, stromal cells, blood vessels, immune cells, fibroblasts and secretory factors (82). A recent study has demonstrated that the interplay between tumor cells and the TME governs tumorigenesis, invasion, metastasis, chemotherapy resistance and the immune response, thereby driving tumor progression and invasion (83). OPN, as a component of the TME, could derive from tumor cells, endothelial cells, fibroblasts and immune cells. OPN exerts an influence on the formation and regulation of the TME (9,84,85). Wei *et al* (36) found that OPN promoted tumor progression by attracting macrophages and activating T cells in the glioblastoma TME. Butti *et al* (86) reported that OPN could remodel the TME immune suppression and promoted tumor progression by modulating the polarization of T helper cells, T-regulatory cells and tumor-associated macrophages. Rogers *et al* (87) reported that myofibroblastic cancer-associated fibroblasts in the TME promoted cancer stem cell proliferation and metastasis, whereas inhibition of OPN in a mouse breast cancer model resulted in diminished tumor stemness. Therefore, destruction of the TME by targeting OPN may effectively inhibit tumor progression.

OPN exhibits distinct effects across various cancer types. For example, OPN inhibits autophagy in colorectal cancer cells, induces breast cancer cell migration and increases angiogenesis in breast cancer, and leads to cell migration and invasion in lung adenocarcinoma (88,89). Further studies elucidating the precise involvement of OPN in cancer pathogenesis are required.

OPN triggers signaling pathways in tumor pathogenesis. The essential role of OPN in tumorigenesis and development is well-established, and OPN exerts its effects by activating multiple intertwined signaling pathways such as the JNK, Ras/Raf/MEK/ERK, PI3K/Akt, Janus kinase (JAK)/STAT, NF-κB and TIAM Rac1 associated GEF 1/Rac1 pathways (14,57). These pathways regulate cell proliferation, adhesion, diffusion, migration, invasion and epithelial-mesenchymal transition (EMT) of tumor cells, as well as immunosuppression and drug resistance (1). The main pathways regulated by OPN that are involved in tumorigenesis and development are summarized and illustrated in Fig. 2 (90-99).

JNK signaling pathway. The JNK signaling pathway has been demonstrated to be activated in various types of cancer such as lymphoma, pancreatic cancer, hepatocellular carcinoma and childhood sarcoma (91). Messex *et al* (100) found that extraneously added OPN activated the JNK pathway, which accelerated cell proliferation and prostate cancer development. Insua-Rodríguez *et al* (101) demonstrated that JNK was activated in breast cancer xenograft tumor mouse models, which enhanced OPN expression, resulting in chemotherapy resistance and metastasis. Li *et al* (102) demonstrated that OPN bound to MB231 breast cancer cells and activated the JNK signaling pathway, which resulted in EMT initiation and cellular migration.

Ras/Raf/MEK/ERK pathway. The Ras/Raf/MEK/ERK signaling pathway serves a vital role in promoting cell proliferation, survival and metastasis in various cancer types (103). Yang *et al* (104) reported that knockdown of OPN in squalene synthase-overexpressing lung cancer cells inhibited their migration and invasion. Chernaya *et al* (105) found that, in thyroid cancer, activation of the RAS-RAF-MEK pathway led to upregulation of OPN and its receptors (integrin), which in turn increased the metastatic potential of tumor cells. Sun *et al* (106) adopted RNA interference (RNAi) to reduce OPN expression, which resulted in a decrease in the expression levels of MMP-2 and inhibition of the MEK/ERK pathway, eventually retarding hepatic carcinoma growth and metastasis.

PI3K/AKT signaling pathway. The PI3K/AKT signaling pathway is aberrantly activated in various types of cancer (91). OPN has been found to activate the PI3K/AKT pathway by binding with CD44, consequently promoting cell proliferation and suppressing apoptosis (107). Zhang *et al* (108) reported that OPN bound with integrin αvβ3 and activated the PI3K/AKT pathway in breast cancer, while knockdown of OPN suppressed breast cancer metastasis. Furthermore, Fu *et al* (109) revealed that upregulation of OPN facilitated chemoresistance of non-small cell lung cancer (NSCLC), while silencing of OPN inhibited the phosphorylation of AKT and ERK, weakening gefitinib resistance in NSCLC cells.

JAK/STAT signaling pathway. The JAK/STAT signaling pathway is overactivated in cancer (110). OPN interacts with CD44 and triggers the activation of JAK protein kinase, which induces STAT phosphorylation and consequent enhanced hepatic carcinoma cell proliferation (111). Behera *et al* (112) demonstrated that OPN activated JAK2/STAT3 signaling and stimulated breast tumor growth in mice. JAK2 inhibitor (AG 490) administration could suppress OPN-induced STAT3 phosphorylation and promote tumor cell apoptosis (112).

NF-κB signaling pathway. The NF-κB signaling pathway has been found to be activated in cancer (104). OPN binding to integrin αvβ3 results in the translocation of NF-κB from the cytoplasm to the nucleus, and promotes tumorigenesis, proliferation, invasion and angiogenesis of HCC (113). Chen *et al* (114) demonstrated that specific small interfering RNA (siRNA) inhibition of OPN could effectively attenuate NF-κB levels, thereby inhibiting proliferation of esophageal squamous cell carcinoma cells and suppressing tumor formation and metastasis. Saurav *et al* (115) reported that inhibition of OPN and/or NF-κB signaling could enhance the efficacy of irinotecan, and the combination of OPN and/or an NF-κB inhibitor with irinotecan may enhance the therapeutic efficacy while reducing the development of drug resistance.

p38 MAPK signaling pathway. The p38 MAPK signaling pathway is a key signal transduction cascade that cells possess in response to environmental stimuli, and has attracted much attention as a promising target for cancer therapy (116,117). Yu *et al* (118) reported that OPN was highly expressed in head and neck squamous cell carcinoma (HNSCC), and OPN promoted the proliferation and invasion of HNSCC cells by activating the p38-MAPK signaling pathway. Huang *et al* (66) stated that OPN participated in the activation of the p38 MAPK signaling pathway, thereby promoting cell migration and invasion of colorectal cancer. OPN-conferred chemoresistance is also associated with the p38 MAPK signaling pathway. Pang *et al* (119) demonstrated that OPN mediated cyclophosphamide resistance in MDA-MB-231 tumor cells by activating p38 MAPK.

4. OPN-based cancer treatment

Cancer is threatening the life of millions of individuals worldwide, and its therapeutics still face great challenges (120). OPN possesses various functions in the context of cancer, including the enhancement of tumor progression and metastasis, inhibition of tumor cell apoptosis, regulation of the TME, and induction of chemotherapeutic drug resistance. OPN represents a promising therapeutic target for the improved treatment of cancer. RNAi, small-molecule inhibitors, aptamers targeting OPN, and blockade binding of OPN and its receptor are expected to be alternative methods for cancer therapy (14,89). Table I outlines available OPN-based therapeutic strategies.

OPN gene interference. siRNAs and short hairpin RNAs (shRNAs) can efficiently downregulate the expression of specific genes. Knockdown of OPN with siRNA represents a promising intervention for various types of cancer such as liver tumors, chronic myeloid leukemia, familial adenomatous polyposis and metastatic melanoma, and it is currently undergoing clinical trial (121). Ben-David-Naim *et al* (122) demonstrated that administration of nanoparticle-encapsulated OPN siRNA effectively reduced OPN expression and suppressed tumor growth in a mouse breast cancer model. Yang *et al* (123) reported that knockdown of OPN with specific siRNA or shRNA could inhibit breast tumor progression. These findings suggest that downregulation of OPN expression could inhibit tumor cell proliferation, migration, invasion, angiogenesis and other processes. Using siRNA technology to silence OPN offers a plethora of strategic opportunities to develop effective treatment modalities against cancer.

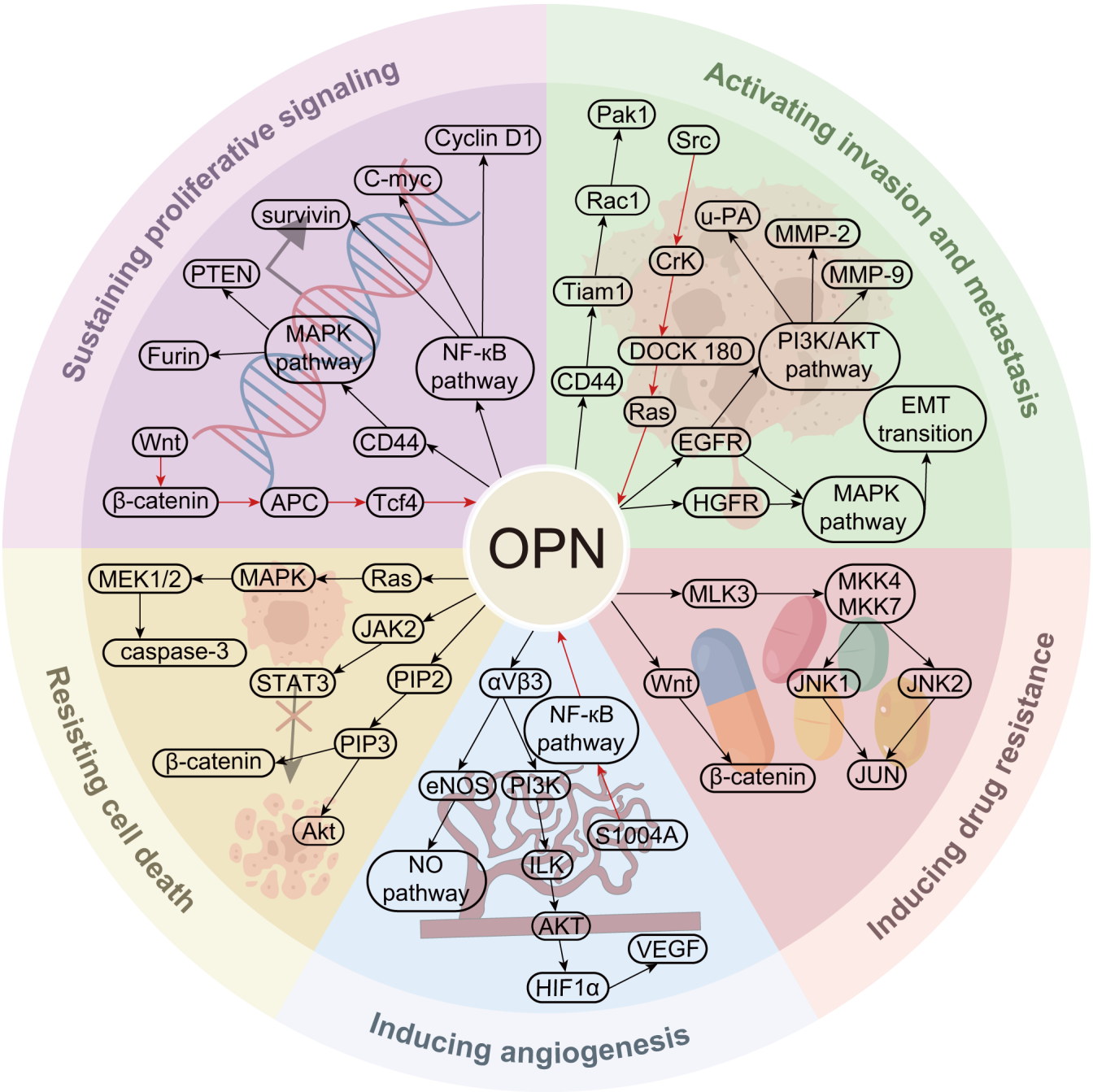

Figure 2. Representative signaling pathways involved in OPN participating in cancer genesis and development. Black arrows indicates that OPN initiates the signaling pathway, while red arrows indicate that the signaling pathway ends with OPN modulation. APC, adenomatous polyposis coli; EMT, epithelial-mesenchymal transition; eNOS, endothelial nitric oxide synthase; HGFR, hepatocyte growth factor receptor; HIF1α, hypoxia-inducible factor-1α; ILK, integrin linked kinase; JAK2, Janus kinase 2; MKK, mitogen-activated protein kinase kinase; MLK3, mixed lineage kinase 3; NO, nitric oxide; OPN, osteopontin; Pak1, p21 (RAC1) activated kinase 1; PIP2, phosphatidylinositol (4,5)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; S1004A, S100 calcium binding protein A4; Tcf4, transcription factor 4; Tiam1, TIAM Rac1 associated GEF 1; u-PA, urokinase-type plasminogen activator.

Small-molecule inhibitors of OPN. Given their compact size and efficient cell membrane permeability, small-molecule inhibitors targeting specific signaling pathways have attracted increasing attention in disease intervention (23,124). Small-molecule inhibitors toward OPN have been applied for cancer treatment. Sharma *et al* (125) demonstrated that inhibition of OPN expression with trichostatin A effectively prevented tumor growth and metastasis in a mouse xenograft model. Androstenedione (Andro), a diterpenoid compound isolated from androsacetum, inhibits OPN expression, resulting in cell cycle arrest and apoptosis of breast cancer cells, as well as tumor-endothelial cell interactions (126). Kumar *et al* (126) further demonstrated that Andro suppressed breast cancer cell proliferation by downregulating c-jun expression and inhibiting PI3K/Akt signaling activation. Parecoxib, a traditional COX-2 inhibitor, has been reported to retard the progression of colorectal cancer by suppressing OPN expression via blockade of the nuclear receptor subfamily 4 group A member 2 and Wnt signaling pathways (17). Matsuura *et al* (127) demonstrated that simvastatin, a high mobility group-CoA inhibitor,

Table I. OPN-based cancer interventions.

First author/s, year	Targeting strategy	Inhibitor	Target molecule(s) and/or related signaling pathways	Application model	Effect/outcome	(Refs.)
Kumar *et al*, 2010	RNAi	siRNA	OPN, CD44, MKK3/6, p38-dependent NF-κB activation	Human cervical cancer cells (HeLa and SiHa), female NOD/SCID mice	OPN silencing causes reduced growth, migration and invasion	(16)
Saleh *et al*, 2016		siRNA	OPN	Murine mammary tumor cells (RM11A, RJ348 and RJ345)	Inhibits cancer cell proliferation, apoptosis, migration and invasion	(141)
Zhang *et al*, 2014		siRNA	OPN, LC3, Beclin1, PI3K/Akt/mTOR pathway	Human breast cancer cells (MDA-MB-231)	Knockdown decreases the activation of the PI3K/Akt/mTOR pathway, inhibits migration and invasion, and induces autophagy in cancer cells	(108)
Cho *et al*, 2015		siRNA	OPN, PSOT	Human lung adenocarcinoma epithelial cell line (A549), large cell lung carcinoma cancer cell line (H460), male nude mice (BALB/c-nu)	siOPN treatment reduces tumor size and weight	(142)
Bhattacharya *et al*, 2010		miRNA	OPN, miRNA 181a	HCC cell lines (Hep G2 and Hep 3B)	OPN expression is regulated by miRNA 181a, and the presence of siOPN attenuates the adhesion, migration and invasion of tumor cells	(143)
Zagani *et al*, 2009	Small-molecule inhibitors	Parecoxib (COX-2 inhibitor)	OPN, Wnt/β-catenin pathway	Mouse colon adenocarcinoma (CT26) $Apc^{min/+}$ mice	Downregulation of OPN expression by COX-2 inhibitors inhibits tumor growth	(17)
Matsuura *et al*, 2010		Simvastatin (HMG-CoA inhibitors)	OPN, 3-hydroxy-3-methylgluaryl coenzyme A reductase	Human ovarian carcinoma cell lines (RMG-1 and TOV-21G), human adenocarcinoma cell lines (HTOA, MH and KFr), human mucinous adenocarcinoma cell line (MCAS)	Apoptosis, growth arrest and enhanced invasion were induced by reducing OPN expression	(127)
Kumar *et al*, 2012		Andrographolide	OPN, PI3 kinase/Akt signaling	Human breast adenocarcinoma cell lines (MDA-MB-231 and MCF-7), mouse fibroblast cell line (NIH-3T3)	Inhibition of cancer cell proliferation, adhesion, apoptosis, migration and invasion	(126)
Sharma *et al*, 2010		Trichostatin A (histone deacetylase inhibitor)	HDAC1 inhibitor, OPN, c-Jun, cyclin D1, u-PA	Human cervical carcinoma cells (HeLa and SiHa), female NOD/SCID mice	Cancer cell cycle arrest, stimulates differentiation and induces apoptosis	(125)

Table I. Continued.

First author/s, year	Targeting strategy	Inhibitor	Target molecule(s) and/or related signaling pathways	Application model	Effect/outcome	(Refs.)
Lv *et al*, 2013		Curcumin + BPS	OPN, CD44, MMP-9	Human ovarian cancer cells (SKOV3)	Reduces invasion of ovarian cancer and dendritic cells	(128)
Mason *et al*, 2008		Agelastatin A	β-catenin, Tcf4 signaling	Mammary epithelial cells (MDA-MB-231 and MDA-MB-435s)	Inhibits OPN-mediated invasion, adhesion and colony formation of malignant cells	(144)
Mi *et al*, 2009	Aptamers	OPN-R3	OPN, JNK1/2, PI3K	Human breast cancer cells (MDA-MB-231)	OPN-R3 effectively inhibits adhesion, migration and invasion of cancer cells	(15)
Dai *et al*, 2010	Blocking antibodies	Anti-OPN antibody	OPN, hu1A12	Human breast cancer cells (MDA-MB-435S)	Inhibition of cancer cell proliferation, survival, adhesion, migration and invasion potential	(145)
Ahmed and Kundu, 2010		Anti-αvβ3 integrin antibody	αvβ3-integrin	Breast cancer cells (MCF-7 and MDA-MB-468)	Inhibits OPN-induced tumor growth and angiogenesis	(132)
Teramoto *et a*l, 2005		Anti-CD44 antibody	CD44 receptor	Mouse embryonic fibroblasts (NIH3T3)	Reduces tumor progression induced by OPN	(146)
Moorman *et al*, 2020		AOM1	Blocking the αvβ3 integrin-binding site on OPN	NSCLC tumor-bearing mice	Increases the efficacy of PD-1-based ICB immunotherapy	(61)
Chiou *et al*, 2019	OPN inactivation	OPN	FSTL-1	Lung cancer cell lines (A549, H1299, PC13 and PC14)	OPN inactivation prevents tumor progression	(134)

AOM1, anti-OPN monoclonal antibody; BPS, basilic polysaccharide; COX-2, cyclooxygenase-2; FSTL-1, follistatin-like protein 1; HCC, hepatocellular carcinoma; HDAC1, histone deacetylase 1; HMG, high mobility group; ICB, immune checkpoint blockade; miRNA, microRNA; MKK, mitogen-activated protein kinase kinase; NOD/SCID, nonobese diabetic/severe combined immunodeficient; NSCLC, non-small cell lung cancer; OPN, osteopontin; PD-1, programmed cell death protein 1; PSOT, polysorbitol-based transporter; RNAi, RNA interference; siRNA/si, small interfering RNA; SVVYGLR, serine-valine-valinetyrosine-glutamate-leucine-arginine; Tcf4, transcription factor 4; u-PA, urokinase-type plasminogen activator.

downregulated the expression levels of OPN and αvβ1, αvβ3, α5β1 and α5β3 integrin, accompanied by an enhancement in the invasion of ovarian cancer. Lv *et al* (128) found that combined administration of curcumin and basilic polysaccharides could effectively suppress cell proliferation and invasion by downregulating OPN and its receptor in ovarian cancer.

Aptamers of OPN. Aptamers, as short single-stranded deoxyribonucleic acid or ribonucleic acid molecules, have unique biometric capabilities. They are able to fold to form a three-dimensional conformation and precisely bind to a protein target (129). This process enables the aptamers to bind to specific targets with high selectivity, including proteins, peptides, small carbohydrate molecules and even living cells, showing great potential in biomedical research and diagnostic applications (130). Aptamers exhibit advantages such as high affinity for the target, biochemical stability and low immunogenicity, and could potentially be used as cancer therapeutics (130). Mi *et al* (15) demonstrated that the treatment of MDA-MB-231 breast cancer cells with OPN aptamers, OPN-R3, resulted in inhibition of cell adhesion, migration and invasion. The authors further demonstrated that OPN-R3 inactivated OPN-associated signaling pathways, including the PI3K, JNK1/2, Src and Akt pathways (15). Furthermore, *in vivo*, OPN-R3 administration prevented tumor growth in breast cancer xenotransplantation mouse models (131).

Blocking binding of OPN with its receptors. OPN needs to bind with its receptors to exert its roles in tumor genesis and progression. Therefore, disrupting the binding of OPN and its receptors represents an alternative strategy for tumor treatment. Rangaswami *et al* (90) reported that blocking antibodies against αvβ3-integrin effectively suppressed OPN-induced tumor growth and angiogenesis. Furthermore, αvβ3-blocking antibodies have been found to effectively inhibit OPN-mediated activator protein 1 activation in breast cancer cells (132). Ahmed *et al* (133) showed that administration of CD44 antibody disrupted the interaction between OPN and CD44, consequently restricting OPN-CD44 mediated tumor invasion and metastasis. Blocking the binding of OPN with its receptors offers a novel therapeutic strategy.

OPN inactivation. OPN needs to be cleaved by specific proteases to expose its receptor binding domain in order to exert its function. Therefore, blocking enzyme cleavage could render OPN inactive. Chiou *et al* (134) showed that follistatin-like protein 1 directly bound to the uncleaved form of OPN and inhibited the proteolytic activation of OPN, which blocked OPN-integrin/CD44-related signaling pathways and consequent lung cancer metastasis. Thrombin has been demonstrated to participate in OPN hydrolysis, which is essential for effective binding of OPN with its receptors (135). Peraramelli *et al* (136) reported that a thrombin inhibitor, dabigatran etexilate, retarded B16 melanoma growth by blocking OPN activation. Therefore, inhibiting OPN activation by blocking OPN signaling and proteolytic processing may be a feasible therapeutic approach to stop tumor progression. Current OPN-based interventions are summarized in Table I.

Although OPN is a promising target for cancer therapy, there are still some limitations in practical applications. Gene interference technologies such as RNAi have poor stability and low delivery efficiency, making it difficult to continuously and specifically inhibit OPN expression *in vivo* (137). Small-molecule inhibitors have several drawbacks, including a short half-life, poor oral bioavailability, drug resistance, multiple side effects and high production costs. Off-target effects occur when a molecule in the body binds non-specifically to molecules other than its intended target, which may lead to unexpected biological effects or adverse reactions (138). Blocking the interaction between OPN and receptors is also challenging because OPN can bind to multiple receptors, and single blocking has limited effects, and may also trigger unknown biological effects. Complete inactivation of OPN may affect its normal physiological functions and cause side effects. Despite the limitations of current strategies, each approach has its unique advantages and applicable scenarios (23). In practical applications, appropriate strategies should be selected based on specific diseases and treatment requirements, and their limitations should be overcome through technological innovation and optimization. For example, the therapeutic efficacy and safety can be effectively improved by optimizing aptamer design, improving delivery systems and enhancing the bioavailability of small-molecule inhibitors (89).

The combination of multiple therapeutic strategies could provide more comprehensive and effective treatments, and a representative combination is OPN inhibitors together with immune checkpoint intervention. Lu *et al* (139) found that administration of the WD repeat domain 5 protein (WDR5), an inhibitor of OPN, suppressed the growth of orthotopic pancreatic tumors in mice. Furthermore, WDR5 enhanced the efficacy of anti-programmed cell death protein 1 immunotherapy in inhibiting pancreatic tumor growth in mice (139). Zhu *et al* (140) reported that OPN expression in HCC was positively associated with the programmed death-ligand 1 levels, whereas OPN knockout enhanced the antitumor function of T-helper 1 cells. Future research should focus on mechanism verification and optimization of multi-target combination strategies to achieve more precise antitumor treatment.

5. Summary and perspectives

OPN, as a secretory protein, is aberrantly expressed in various types of cancer and exhibits a crucial role in both the pathogenesis and progression of cancer. OPN exerts an oncogenesis-promoting effect by stimulating cell proliferation, antagonizing apoptosis, promoting angiogenesis, suppressing immunity and inducing drug resistance. Given its pivotal role, OPN has been regarded as one of the targets for cancer treatment. OPN-based cancer therapeutics based on gene interference, inhibitors and immunoregulation have displayed great potential in research and clinical settings. However, a few aspects deserve to be considered to broaden OPN-based cancer interventions. Firstly, the molecular pathways through which OPN participates in tumorigenesis could be revealed by multiple-omics analysis. Secondly, the dynamic changes of OPNs during cancer development and treatment should be precisely monitored. Thirdly, OPN-based therapeutics should be combined with other treatment strategies. In summary, by

elucidating the various roles of OPN in cancer genesis and development, the present review could deepen the understanding of cancer biology and help develop a more effective cancer treatment strategy.

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Authors' contributions

CZ proposed the concept and edited the draft. WX and ZB wrote original draft. FF, LL and LC reviewed and finalized the draft. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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