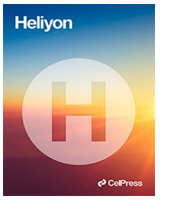
Heliyon 9 (2023) e21055

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Role of osteopontin in cancer development and treatment

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ARTICLE INFO

Keywords:
Osteopontin
Colorectal cancer
Tumor therapy
Tumor microenvironment
Macrophages

ABSTRACT

Osteopontin (OPN) is a multifunctional protein secreted intracellularly and extracellularly by various cell types, including NK cells, macrophages, osteoblasts, T cells, and cancer cells. Owing to its diverse distribution, OPN plays a role in cell proliferation, stem-cell-like properties, epithelial–mesenchymal transformation, glycolysis, angiogenesis, fibrosis, invasion, and metastasis. In this review, we discuss recent findings, interpret representative studies on OPN expression in cancer, clarify that elevated OPN levels are observed in multiple cancer types (including colorectal, breast, lung, and liver cancer), and explore how OPN-macrophage interactions shape the tumor microenvironment. We also summarize progress in OPN research with regard to tumor therapy, which can facilitate the development of novel anti-tumor treatment strategies.

1. Introduction

The review investigates the structure, function, and variants of osteopontin (OPN), also known as secreted phosphoprotein 1 (SPP1).

1.1. Structure and function of OPN

OPN also known as SPP1, is the main salivary protein that regulates bone formation and remodeling in bone tissue [1,2]. OPN is closely associated with early T lymphocytes activated protein 1 (ETA1) and bone sialoprotein 1(BSP1) [3]. The gene locus of OPN contains the arginine-glycine-aspartic acid (RGD) sequence, which can bind to various integrins [4,5], including αvβ1, αvβ3, αvβ5, αvβ6, and others. OPN interacts with integrin αvβ1 and regulates the expression of C/EBPs, inhibiting adipogenic differentiation while promoting osteogenic differentiation of mesenchymal stem cells (MSCs) [6]. When combined with αvβ3, OPN activates the PI3K/pAkt/NF-κB pathway, regulates the NF-κB/ZEB-dependent epithelial–mesenchymal transition (EMT) signal, and promotes tumor development [7]. Additionally, the SVVYGLR domain (non-RGD domain) of OPN can bind to α9β1, α4β1, and γ4β7. These interactions between OPN and α9β1 integrin activate the ERK and p38 signaling pathways, stimulate COX-2 expression in macrophages, and induce angiogenesis [8]. Furthermore, OPN promotes leukocyte adhesion through α4β1 integrin [9]. OPN binds to various forms of CD44, such as the CD44 standard type (CD44s) and CD44v [10]. CD44v6 and CD44v are considered important structures of

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https://doi.org/10.1016/j.heliyon.2023.e21055
Received 19 July 2023; Received in revised form 6 October 2023; Accepted 13 October 2023
Available online 14 October 2023

OPN that promote cancer invasion. They have been identified as protein markers for metastatic behavior in colorectal, gastric, hepatocellular, and breast cancers [11–14].

1.2. Variants of OPN

The *SPP1* gene, located on chromosome 4 (4q13), encodes OPN [15]. Owing to the alternative splicing of SPP1mRNA, OPN undergoes post-translational modifications, such as proteolysis, glycosylation, tyrosine sulfation, and serine/threonine phosphorylation, resulting in several types of OPN variants [16]. OPN in cells (iOPN) lacks an N-terminal signal sequence, causing it to persist in the cytoplasm. iOPN negatively regulates toll-like receptor-mediated immune reactions, reducing the production of pro-inflammatory cytokines and thereby hindering the development of liver cancer [17]. In fibroblasts, iOPN co-localizes with hyaluronate–CD44–ERM complexes in the perimembrane region, contributing to cell migration [18]. Within the nuclei of human renal epithelial cells (293 cells), iOPN co-localizes with polo-like kinase 1 and participates in cell replication [19]. iOPN also plays a role in mesenchymal-to-epithelial transformation (MET), which involves the reversal of EMT. This transformation allows highly expressed disseminated tumor cells to revert to normal epithelial phenotypes during the later stages of metastatic dissemination [20]. iOPN represents an unidentified intermediate of the IL-15 signaling pathway, which ensures the steady-state expansion of NK cells. It holds potential as an immunotherapeutic agent for treating infectious diseases or cancer [21]. Secretory OPN (sOPN) includes the full-length isoform OPN-A and two mutually exclusive splice variants lacking exons 5 and 4, known as OPN-B and OPN-C, respectively [22]. OPN-A and OPN-C may synergistically contribute to tumor progression, but OPN-C is presumably more capable of promoting cell invasion [23,24]. Walaszek et al. demonstrated that OPN-C can be used as an indicator of breast cancer precancerous lesion rate and survival rate [25]. The expression levels of the three variants of OPN were increased in gastric cancer (GC) tissue. OPN-B may promote the survival of GC cells by regulating the expression of CD44v and Bcl-2 family proteins. In addition, OPN-C effectively stimulated GC transfer activity by augmenting the secretion of uPa, MMP-2, and IL-8 [26] (Fig. 1).

OPN interacts with integrin and CD44 receptors to mediate the occurrence and development of tumor cells. OPN increases tumor angiogenesis by inducing CD44 receptor and αvβ3 integrin to activate PI3K/Akt, regulate NF-κB/dependent epithelial mesenchymal transition (EMT) signaling, and regulate HIF1α dependent VEGF expression. OPN and αvβ3 integrin can also mediate the expression of metalloproteinases MMP2 and MMP9 through JNK signaling pathway and promote tumor invasion. OPN inhibits adipogenic differentiation and promotes osteogenic differentiation of MSCS by interacting with integrin αvβ1 and regulating the expression of C/EBPs. OPN induces COX-2 secretion through α9β1 integrin activation of ERK and p38, thereby enhancing tumor cell motility and angiogenesis. OPN binds to its receptor α4β1 integrin and induces relapse through phosphorylation of IKKβ, which induces the expression of pro-survival genes of NF-κB and also enhances adhesion between leukocytes.

2. Method

The PubMed database was used to explore eligible studies. The time frame considered for this review was from the establishment of the database to July 19, 2023. Only the studies that were published in the English language were included. The search was conducted using keywords (“OPN” or “SPP1”) and “Cancer”, (“OPN” or “SPP1”) and “Macrophages”, (“OPN” or “SPP1”) and “Treatment”. Retrospective studies, preclinical studies, case reports and studies that were not majorly co-related with the subject of this review were excluded. A total of 117 English articles were included in the present study (Table 1).

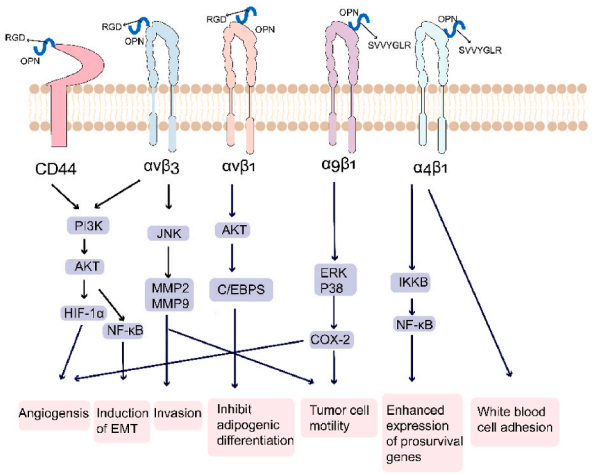

Fig. 1. OPN interacts with integrin and CD44 receptors to mediate the development of tumor cells.

Table 1
The search strategies.

Items	Specification
Date of search	July19 , 2023
Databases and other sources searched	PubMed
Search formula used	("OPN" OR "SPP1") AND "Cancer" ("OPN" OR "SPP1") AND "Macrophages" ("OPN" OR "SPP1") AND "Treatment"
Timeframe	From January 1997 to July 2023
Inclusion and exclusion criteria	Retrospective study, preclinical studies, case report, studies not written in English, The correlation with the study content and the quality of the literature were Excluded
Selection process	Two co-first authors conducted initial screening by title and abstract. The included articles were read in full text. Eventually, all the authors participated in the discussion and received the same opinion

3. Results and discussion

3.1. Role of OPN in various types of cancer

3.1.1. Role of OPN in colorectal cancer

Colorectal cancer (CRC) is the most common cancer after lung and breast cancer [27] and ranks fourth in cancer-related mortality [28]. Notably, the incidence of CRC in China is increasing, and the age of onset is decreasing [29]. Although surgical treatment, chemotherapy, drug therapy, and immunotherapy have improved patient outcomes, the mortality and recurrence rate in patients with CRC remains very high. Currently, the mechanism by which OPN promotes the occurrence and development of CRC remains unclear. However, studies have shown that OPN increases the migration and invasion of CRC cells in a concentration-dependent manner [30]. Additionally, OPN induces the activation of the downstream PI3K-AKT-GSK/3b-b/catenin pathway in CRC cells. Notably, the knockout of highly expressed OPN in CRC significantly inhibits cell proliferation and migration [25]. Furthermore, Chang et al. reported that tumor cell debris in CRC accelerates tumor growth by stimulating OPN production by macrophages in tumor cells and the host microenvironment [31]. Amilca-Seba et al. demonstrated that Slug can directly regulate OPNs at the promoter level, suggesting that OPN can serve as a biomarker to evaluate the invasive phenotype of CRC [32]. Lastly, OPN inhibits autophagy in CRC cells by activating the p38 MAPK signaling pathway [33].

3.1.2. Role of OPN in breast carcinoma

Breast cancer (BRC) is the most common type of cancer and the leading cause of death among women worldwide [34]. China has the highest number of patients with BRC worldwide [35,36]. Studies have shown that OPN expression is increased in BRC. The increased concentration of OPN is associated with tumor invasiveness, disease progression, and reduced survival [37,38]. OPN, when combined with the receptors CD44 and avb3, activates breast fibroblast inflammation and promotes tumor growth [39]. Pio et al. reported that SPP1 may promote breast cancer cell migration and stem-like behavior ["stem-like" cells also known as "cancer stem cells" (CSCs)] by activating the WNK-1 and PRAS40-related pathways [40]. Sample stem cell behavior in vitro shows proliferation, migration, adhesion, and invasion, indicating their potential to transfer into the body [41]. Similarly, OPN promotes BRC metastasis by activating the JNK signaling pathway. Furthermore, OPN can activate the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways, leading to VEGF secretion in endothelial cells and promoting angiogenesis [42,43]. Raineri et al. demonstrated that OPN-triggered ICOSL (B7–H2, CD275, belonging to the B7 family) could induce BRC cell migration and increase angiogenesis both in vivo and in vitro [44].

3.1.3. Role of OPN in non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is the main type of lung cancer and the leading cause of cancer-related mortality globally [45]. Despite recent advances in the treatment of NSCLC, the mortality rate from NSCLC remains high [46]. Studies have shown that OPN is highly expressed in NSCLC and possesses significant metastasis and invasion potential [47,48]. Zhang et al. found that the combination of lipopolysaccharide (LPS) and lipoteichoic acid (LTA) could significantly activate SPP1 and up-regulate the expression of αVβ3 [49]. Activation of the downstream ERK and FAK/AKT signaling pathways promotes NSCLC [50]. Additionally, OPN activates the RON signaling pathway, thereby facilitating migration and invasion of NSCLC cells [51]. Moreover, it promotes the progression of NSCLC cells and mediates drug resistance via the MAPK signaling pathway [52]. SPP1+ tumor-associated macrophages (TAMs) are closely related to the endothelial cells and fibroblasts associated with NSCLC, thereby regulating the tumor microenvironment (TME) [53]. OPN induces the accumulation of VEGF and stimulates neovascularization through autocrine and paracrine mechanisms, thereby promoting NSCLC growth [54]. SPP1 acts as a promoter of EMT, which leads to cell migration and invasion in lung adenocarcinoma (a common subtype of NSCLC) through the upregulation of COL1A1 [55].

3.1.4. Role of OPN in liver cancer

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It is responsible for 790,000 deaths globally annually [56]. Owing to its high recurrence and intrahepatic metastasis rates after surgical resection and poor prognosis,

understanding the mechanism behind HCC progression holds high clinical significance [57,58]. In patients with HCC, elevated levels of OPN are closely associated with liver function deterioration and positively correlated with tumor stage. Therefore, OPN levels are effective diagnostic biomarkers [59]. Evidence suggests that the detection performance of OPN in HCC is superior to that of alpha-fetoprotein (AFP) in the preclinical stage; however, diagnostic tests involving OPN and AFP significantly improve clinical diagnostic accuracy [60]. The combination of OPN and CD44 induces the expression of Twist (a major regulator of EMT, which is crucial for tumor metastasis). This activation occurs through the PI3K/AKT signaling pathway, promoting EMT and HCC metastasis [61,62]. In HCC cells, OPN plays a central role in angiogenesis and supports the formation of the TME [63]. OPN promotes glycolysis of HCC by activating αvβ3-NF-κB signaling [64]. The acidic TME derived from glycolysis is closely associated with tumor metastasis and immune response [65]. Additionally, OPN promotes the progression and metastasis of HCC by activating CCR1 expression, while miR-196a reduces downstream OPN by targeting Runx2 expression. Thus, EMT regulatory factors, such as Slug and Twist, are activated, further driving the aggressiveness of HCC [66,67] (Fig. 2).

The role of OPN in cancer. OPN plays an important role in the occurrence and development of tumors through different mechanisms. In colorectal cancer, OPN stimulates macrophages to maintain M2 phenotype by activating PI3K-AKT-GSK/3b-b/catenin and P38 MAPK signaling pathways, and the expression of SLUG is closely related to OPN. OPN can promote angiogenesis in breast cancer by activating WNK-1, PRAS40, JNK and other signaling pathways and binding to integrin and CD44 receptors. It can promote tumor angiogenesis by activating αvβ3-NF-κB signaling pathway, Slug and Twist in liver cancer. In non-small cell lung cancer, VEGF, COL11A1 and other angiogenic factors are highly expressed by activating FAK/AKT, ERK, RON, MAPK signaling pathways.

3.2. OPN and macrophages

The TME comprises a structural framework of tumor tissue consisting of stromal cells, such as connective tissue cells, vascular components, and immune cells. These components play a critical role in tumor metastasis and progression. Immune cells present in the microenvironment include macrophages (Mφ), lymphocytes, monocytes, and dendritic cells (DC), along with immune checkpoint molecules, such as programmed cell death-1 (PD-1) and programmed cell death ligand 1 (PD-L1) [68]. TAMs are the predominant inflammatory cells infiltrating the TME [69], and their high infiltration is closely related to various tumors [70]. In recent years, inflammation in the TME has gained recognition as a cancer marker [26]. OPN is a pro-inflammatory molecule that regulates the function of all types of immune cells within the TME [71]. In addition, OPN can be activated by matrix metalloproteinases (MMPs), resulting in the formation of smaller pro-inflammatory molecules. OPN production is closely related to the enzyme cyclooxygenase 2 (COX2), which induces inflammation [72].

3.2.1. OPN maintains the M2 phenotype of macrophages and promotes tumor-related processes

TAMs can be categorized into anti-tumor M1 and pro-tumor M2 phenotypes. Once TAMs originating from peripheral blood mononuclear cells are recruited into the TME by tumor-secreted attractants, they experience M1-like or M2-like activation in response to diversified stimulation [[73,74]]. Wei et al. proposed that OPN is a potent chemotactic factor for Mφ, and blocking OPN markedly weakens the ability of glioma cells to recruit Mφ [75]. In lung cancer, Zhang et al. found that SPP1 plays a vital role in the crosstalk between NSCLC cells and TAMs and that the M2 phenotype promotes the migration of NSCLC cells [76]. Additionally, OPN can activate PD-L1 expression in HCC Mφ through the cSF1-cSF1r pathway [77]. Tumor-derived SPP1 can induce M2 reprogramming through the integrin and protein tyrosine kinase 2 (PTK2)-Akt signaling pathways [78].

Interestingly, OPN recruits monocytes, which subsequently differentiate into TAMs [68]. Recent studies have shown that SPP1 (OPN) can bind to CD44 on macrophages, leading to the polarization of TAMs into the M2 phenotype in HCC cells [79]. A distinct TAM subtype, known as SPP1+ macrophages, was recently reported as a potential target against tumor growth and metastasis owing to its

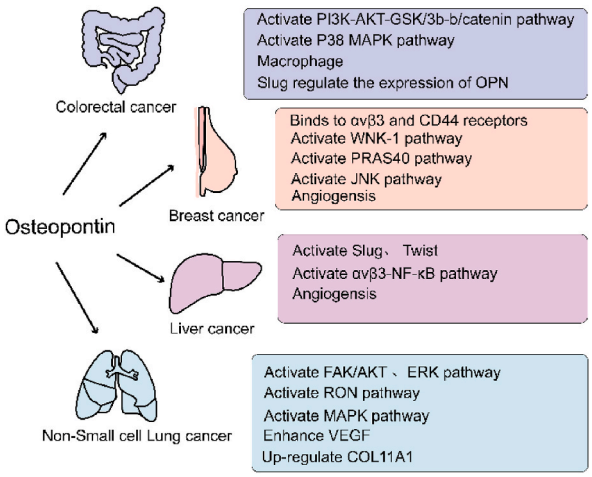

Fig. 2. The role of OPN in cancer.

immunosuppressive properties and positive correlation with EMT markers [80]. Jiang et al. found that SPP1+ macrophages interact with endothelial cells through VEGFA-VEGFR1/Vegfr2 and promote angiogenesis [81]. LIU et al. proposed that the spatial structure of the tumor immune barrier (TIB), composed of SPP1+ macrophages and cancer-associated fibroblasts (CAF), is associated with blocking immune checkpoints, thus limiting immune infiltration of the tumor core [82]. Qi et al. also suggested that cancer-associated fibroblast subtypes (FAP + fibroblasts) and SPP1+ macrophages contribute to extracellular matrix(ECM) remodeling and cooperate to form a desmoplastic microenvironment [83]. SPP1+ TAMs are mainly present in liver metastases(MetS) and show high pro-angiogenic ability [84]. SPP1+ TAMs are closely associated with tumor-associated endothelial cells and fibroblasts, thereby regulating the TME [85,86]. Li et al. observed that SPP1+ TAMs exhibited overall pro-tumor features, including reduced inflammation, phagocytosis, and increased angiogenesis [87].

3.2.2. *Effect of OPN-CD44 axis on macrophages in tumor development*

In the analysis of cell–cell interaction, the presence of SPP1–CD44 was identified within the SPP1-Mφ cluster [53]. The binding of SPP1 (OPN) to the CD44 receptor on macrophages forms the SPP1–OPN axis, which is considered a unique interaction between macrophages and HCC malignancy [88]. The activation of H3K4me3 may promote the immune evasion of pancreatic cancer by activating the OPN–CD44 axis, thereby accelerating the growth and progression of pancreatic cancer [89]. The activation of OPN/CD44 signaling is closely associated with CD8+T cell dysfunction, initiation of metastasis, and promotion of tumor growth [[87,90,91]]. OPN inhibits CD8+T cells from producing IFN-γ and promotes tumor immune tolerance and evasion in colorectal cancer [92] (Fig. 3).

OPN in the tumor microenvironment interacts with macrophages. OPN is a potent chemotactic factor for macrophages, and Tams derived from peripheral blood monocytes are recruited by OPN to the TME and undergo M2-like activation. A unique interaction formed between the OPN-CD44 axis of macrophages and malignancy. OPN can also inhibit the production of IFN-γ by CD8+T cells and promote tumor immune escape.

3.3. *Treatment*

Numerous therapies target OPN, including targeted inhibition of OPN expression at the transcriptional and protein levels, blockade of its receptor and upstream and downstream pathways, OPN inhibitors, and immune checkpoint blockade. However, further studies are needed to bridge the gap between experimental findings and clinical practice (Fig. 4).

3.3.1. *Immunotherapy*

PD-1 receptor and PD-L1 are two astrocytic molecules responsible for T cell-mediated anti-tumor immune responses. Although PD-1/PD-L1 immune checkpoint blocking has been clinically successful, less than a quarter of the treated patients achieve a lasting response, suggesting that the inefficacy may be closely related to immunosuppression in infiltrating cells [[90,93]]. OPN also acts as an immune checkpoint. In colorectal cancer, OPN induces T cell suppression and inhibits CD8+T cells to produce IFN-γ, thereby promoting host tumor immune tolerance and tumor immune avoidance [92]. Lu et al. showed that the gene SPP1, encoding the OPN protein and its receptor, is highly enriched in H3K4me3 in the pancreatic cancer genome, which promotes immune evasion and anti-PD-1 immunotherapy in pancreatic cancer [89]. Qi et al. found that patients with high SPP1 expression or FAP were treated only with anti-PD-L1, and the therapeutic effect was not ideal. Therefore, improving immunotherapy by disrupting the interactions between SPP1+ macrophages and FAP + fibroblasts is a potential therapeutic strategy [83].

3.3.2. *OPN neutralizing antibody therapy*

OPN neutralizing antibody or synthetic peptide directly targets OPN and its receptor CD44, as well as the interaction between αvβ3 integrin and OPN with high safety [94]. In vivo, the anti-OPN antibody exhibits anti-angiogenic effects, suggesting that OPN could

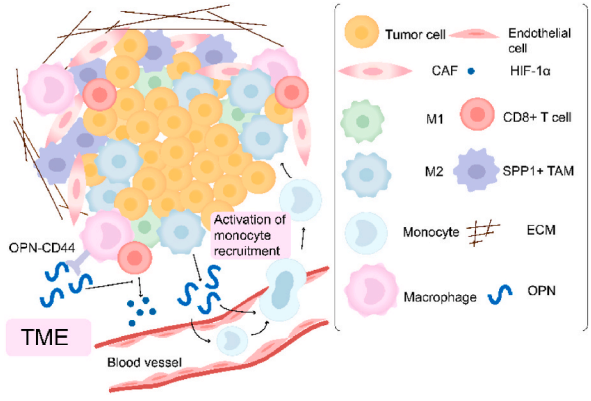

Fig. 3. OPN interactions with macrophages in the tumor microenvironment.

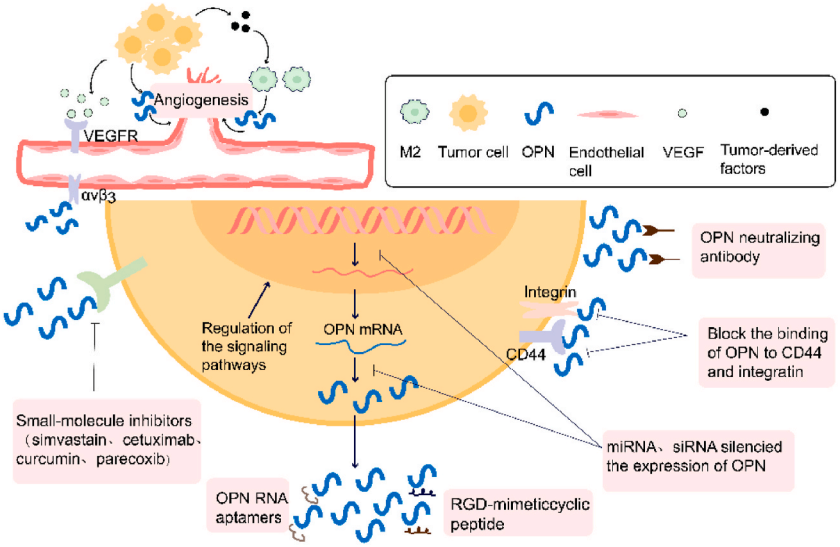

Fig. 4. New strategies for the treatment of OPN.

serve as a potential target for the development of novel anti-angiogenesis therapies in cancer treatment [43]. These OPN-neutralizing antibodies may neutralize some of the tumor-promoting effects of Slug in patients with advanced CRC [33]. In BRC, the use of osteoclast precursors and OPN-neutralizing antibodies reduces osteoclast differentiation and bone metastasis [95]. The OPN-neutralizing monoclonal antibodies 100D3 and 103D6 inhibit colonic neoplasm growth and hold great potential in cancers treated with anti-PD-1 immunotherapy [96]. AOM1 is a type of anti-OPN monoclonal antibody that blocks the integrin αvβ3 connection site and thrombin cracking site on OPN. AOM1 treatment effectively inhibits the expression of αvβ3 and suppresses tumor cell migration [96]. Moreover, anti-OPN monoclonal antibody combined with anti-PD1 was more effective than anti-PD1 immunotherapy alone in inhibiting tumor growth [97].

3.3.3. Epigenetic therapy

Therapeutic approaches based on epigenetic modulators, such as small interfering RNA (siRNAs) and microRNAs, hold great promise for effectively treating various cancers. These modulators bind to their targets and effectively silence genes. Currently, there are ongoing clinical tests to assess their efficacy [98]. miR-181c plays a role in regulating the sensitivity of breast carcinoma cells to adriamycin by downregulating OPN expression [99]. In experiments where miR-196a was knocked down, OPN expression decreased, leading to a marked inhibition of lung metastasis in HCC [67]. Moreover, intra-tumoral injection of siRNA against OPN inhibits breast tumor growth and angiogenesis. In a study by Cho et al. PSOT, a novel gene vector delivering siRNA, effectively silenced OPN expression, leading to the inhibition of NSCLC growth. This finding suggests that PSOT may have a potential in anti-lung cancer therapy [100]. Therefore, combining epigenetic modulators that inhibit OPN splicing or other tumor-specific splicing pathways with conventional chemotherapy could be an effective strategy to prevent tumor progression and recurrence [98].

3.3.4. Small molecule inhibitors targeting OPN

Small-molecule inhibitors play a significant role in specifically targeting certain signaling pathways associated with cancer progression. Their small volume and easy accessibility to the tumor site contribute to their importance. For example, luteolin can inhibit OPN targets and induce the apoptosis of cancer cells through a caspase-dependent pathway, which has anticancer effects [101]. In prostate cancer, curcumin regulates VEGF expression through the OPN/αvβ3 pathway, which possesses anti-angiogenic and anti-tumor invasion properties [72]. In breast cancer, andrographolide (Andro) decreases the expression of OPN and inhibits the interaction between endothelial cells and the tumor by suppressing the expression of c-jun and activating PI3K/Akt [102]. In addition, the binding of OPN to the αvβ3 receptor induces the activation of Rho GTPase, which is inhibited by bisphosphonates (BPs), attenuates the CD44/MMP-9 interaction on the cell surface, and suppresses the migration of prostate cancer cells [103]. Blocking NR4A2 and Wnt signaling by downregulating OPN with a parecoxistep reduces colon cancer risk [104]. Moreover, IL-33 may play an anti-tumor role during early cetuximab treatment by inhibiting OPN expression [105]. Simvastatin can reduce OPN expression by inhibiting the IL-13-activated STAT6 pathway [106].

3.3.5. Targeting CD44 and integrin receptor therapy

MI et al. showed that targeting CD44 resulted in an OPN-mediated reduction in tumor growth. Additionally, blocking the interaction between OPN and integrin αvβ3 resulted in a decreased expression of ILK, urinary plasminogen activator, and MMP-2 in mouse mammary gland epithelial cancer cells [107]. In a study conducted by Robertson et al. it was found that OPN binds to CD44 or αvβ3 receptors in PC3 cells via the Akt pathway, resulting in differential effects on the proliferation and survival of prostate cancer cells

[108]. By functioning as an aptamer of OPN RNA, OPN-R3 can reduce the combination of OPN, αvβ3 and CD44 on the surface of human mammary carcinoma cells. This inhibition ultimately reduces local invasion and distant metastasis in a breast cancer xenotransplantation model. The mechanism behind this effect involves the induction of JNK1/2, Src, and PI3K-Akt signaling by OPN-R3 [109].

3.3.6. Angiogenesis and therapy

Inhibition of angiogenesis is one of the major treatment strategies for cancer. A new strategy for personalized cancer treatment involves combining VEGF-targeted antiangiogenic therapy with the blocking of other pro-angiogenic factors [110]. Angiogenesis involves the activation, proliferation, and migration of ECs. Studies have shown the significant role of the integrin family in tumor angiogenesis [111]. The first integrin to be discovered as a regulator of angiogenesis was αvβ3, which exhibits high expression levels associated with tumor angiogenesis [112]. In response to stimulation by tumor-derived angiogenic factors, αvβ3 expression is elevated and interacts with multiple ECM proteins, such as OPN, to promote angiogenesis and metastasis [113]. OPN activates the I-Kappa-B kinase (IKK)/NF-Kb signal cascade to induce COX-2 expression, which regulates the production of prostaglandin E2 (PGE2) and leads to COX-2/PGE2-stimulated angiogenesis. VEGF is a marker of hypoxia and angiogenesis [114]. Vergis R. et al. discovered that OPN expression was closely correlated with the expression of hypoxia-inducible factor-1α (HIF-1α) and VEGF [115]. OPN can induce integrin kinase (ILK)/AKT-mediated NF-kB activation under hypoxic conditions, leading to HIF1α-dependent VEGF expression and angiogenesis in human BRC specimens [116]. TAMs are key inducers of angiogenic switching in animal tumor models. OPN can directly or indirectly activate tumor angiogenesis in vivo and in vitro in mouse tumor models [117]. OPN-induced VEGF enhanced VEGFR-2 phosphorylation and angiogenesis in endothelial cells [54].

New strategies for the treatment of OPN. Small molecule inhibitors, siRNA, miRNA, and OPN neutralizing antibodies were used to target OPN and disrupt the interaction of OPN with integrin and CD44 and inhibit angiogenesis.

4. Conclusion

The findings suggest that OPN is a potential therapeutic target for various cancers and may serve as a valuable diagnostic or prognostic marker for specific cancer types. However, further research is needed to fully understand the underlying mechanisms of OPN in cancer development and progression. In macrophages, OPN can maintain the M2 phenotype and promote its formation. In recent years, the SPP1 (OPN) + TAM model has provided new perspectives in cancer immunotherapy. OPN can be used as a new immune checkpoint to supplement the limitations of PD-L, PD-L1, and other immune checkpoints as it has been noted that a combination of an anti-OPN monoclonal antibody and anti-PD1 is more effective in inhibiting tumor growth. However, application of OPN in cancer therapy still remains at a nascent stage because of the lack of research in this field Therefore, extensive research is needed to establish OPN as a new target for cancer treatment.

Funding statement

This work was supported by the College Students' Innovation and Entrepreneurship Training Program (No: 202213705030, S202213705062) and Sichuan Provincial Administration of Traditional Chinese Medicine (no. 2021MS101, 2021MS508).

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Zhihua Yan: Investigation, Methodology, Visualization, Writing – original draft. **Xue Hu:** Software, Writing – original draft, Writing – review & editing. **Bin Tang:** Funding acquisition, Writing – review & editing. **Fengmei Deng:** Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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