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Osteopontin and its downstream carcinogenic molecules: regulatory mechanisms and prognostic value in cancer progression

Minireview

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Osteopontin (OPN) is a multifunctional phosphorylated glycoprotein that is expressed at significantly elevated levels in various cancers. OPN overexpression is closely associated with the development of cancer progression such as proliferation, metastasis, angiogenesis, apoptosis resistance, drug resistance, and immunosuppression, and may also be an independent prognostic biomarker for a variety of cancers. This review broadly summarizes the mechanisms that regulate the expression of downstream oncogenic molecules after OPN binds to integrin receptors or CD44 receptors, which involve a complex intracellular "signaling traffic network" (including key kinases, signaling pathways, and transcription factors). In addition, we review the prognostic value of OPN, OPN synergistic downstream oncogenic molecules in the female breast, non-small cell lung, prostate, colorectal, gastric, and hepatocellular carcinomas. The prognostic value of OPN in tissues or blood may vary due to differences in study subjects or detection methods, and this aspect of the study requires further systematization with a view to applying the detection of OPN to clinical applications. Importantly, based on the fact that the oncogenic effect of OPN correlates with the expression of the above-mentioned oncogenic molecules, this work may provide some help in the study of combination therapy targeting OPN and the above-mentioned oncogenic molecules.

Key words: osteopontin, mechanisms, oncogenic molecules, prognostic value, cancer

According to the 2020 Global Cancer Data Statistics, there is an estimated 19.3 million new cancer patients and nearly 10 million cancer deaths worldwide, and cancers with high incidence and mortality include female breast cancer, lung cancer, colorectal cancer, prostate cancer, gastric cancer, and liver cancer [1]. Although various combined treatment modalities such as surgical resection, chemotherapy, radiotherapy, immunotherapy, and molecular targeted therapy are applied to most cancer patients, the survival rate and prognosis are poor due to high surgical recurrence rate, frequent lymph node and distant metastases, and the lack of effective prognostic biomarkers and therapeutic targets, which bring heavy economic burden to the society and patients [2]. Therefore, it is necessary to find better predictable biomarkers and valuable therapeutic targets for them.

Osteopontin (OPN) is a phosphorylated glycoprotein of the extracellular matrix (ECM) that transmits information between matrix and cells and between cells and cells [3]. In recent years, OPN has been widely studied in cancer progression. It has been demonstrated that OPN is overexpressed in various malignancies such as breast cancer, non-small cell lung cancer (NSCLC), prostate cancer, gastrointestinal malignancies, genital malignancies, malignant melanoma, and malignant glioma, and it is closely associated with cancer invasion, metastasis, angiogenesis, and the development of immunosuppression [4–6]. According to existing studies, OPN recognizes and binds mainly to integrin receptors and CD44 receptors, which trigger the activation of phosphorylation of various kinases and the expression of transcription factors in cells [7–9]. These kinases and transcription factors form a complex intracellular "signaling traffic network", which ultimately regulates the expression of several carcinogenic molecules, such as vascular endothelial growth factor (VEGF) [10], hypoxia-inducible factor-1α (HIF-1α) [11],

epithelial-mesenchymal transition (EMT)-related proteins [12], matrix metalloproteinase-1/2/7/9 (MMP-1/2/7/9) [7, 13, 14], urokinase type plasminogen activator (uPA) [15], apoptosis-related proteins [16], and other molecules. Therefore, it is of far-reaching significance to understand the mechanism by which OPN regulates downstream carcinogenic molecules. For a long time, studies on OPN in cancer prognosis have also been an important focus, and OPN may be an independent predictive biomolecule for a variety of cancers, closely associated with treatment responsiveness, clinical or pathological staging, metastasis, recurrence, and survival [4]. In addition, the joint prediction of OPN and downstream carcinogens may better highlight the key role of OPN in cancer prognosis. In this review, the authors focus on the intracellular "signal traffic network" regulated by OPN and the expression of downstream carcinogenic molecules. We also analyze the prognostic value of OPN, OPN and downstream carcinogenic molecule combinations in patients with breast cancer, NSCLC, prostate cancer, colorectal cancer, gastric cancer, and hepatocellular cancer (HCC).

Molecular structure, typing, and receptors of OPN

In 1979, Senger et al. first reported a phosphorylated protein associated with malignant transformation [17]. Later, Franzen et al. first isolated and identified a similar secreted ECM protein from the bovine bone matrix and named it OPN [18]. OPN belongs to a multifunctional type of phosphorylated glycoprotein, also known as secretory phosphorus protein 1 (SPP1), bone sialoprotein-1 (BSP-1), and early T-lymphocyte activation 1 (Eta-1) [19]. Studies have confirmed that OPN is mainly secreted by osteoclasts, osteoblasts, vascular endothelial cells, smooth muscle cells, cardiomyocytes, fibroblasts, and various immune cells, which are distributed in various tissues or body fluids of the human body [9, 12]. OPN is involved in a variety of physiological and pathological diseases, including bone tissue metabolism, wound healing, vascular calcification, inflammatory response, atherosclerosis, diabetes, cancer, and so on [9, 19].

Molecular structure and typing of OPN. In recent years, we have obtained an in-depth understanding of the structure of the human OPN gene, which is localized on human chromosome 4q21-q25 and encoded by the single-copy gene SPP1 [20]. OPN is composed of approximately 314 amino acids in a single chain polypeptide structure, including 7 exons and 6 introns [9]. Studies have demonstrated that OPN mainly consists of arginine-glycine-aspartic acid (RGD) binding domain, serine-valine-valine-glutamate-leucine-arginine (SVVYGLR) binding domain, CD44 receptor binding domain, MMP cleavage site binding domain, thrombin cleavage site binding domain, heparin binding domain, and calcium binding domain, which are the basis of various biological functions of OPN [3, 9, 19]. Depending on the needs of tissues and organs, OPN undergoes a series of modification behaviors such as phosphorylation, glycosylation, and sialylation at the post-translational level, which results in the molecular weight of OPN proteins varying between 41–75 kDa and may also be the basis for the functional diversity of OPN proteins [19]. In addition, according to the number of exons, OPN is divided into 5 splicing variants: OPN-a, OPN-b, OPN-c, OPN-4, and OPN-5. OPN-a is full-length splicing, containing 7 exons; OPN-b is missing exon 5; OPN-c is missing exon 4; OPN-4 is missing exons 4 and 5; and OPN-5 contains an additional exon, located between exons 3 and 4, which will produce alternative translation [9]. The biological functions of OPN-a, OPN-b, and OPN-c are now gradually understood, and they have their own unique expression and biological functions in different cancers. For example, OPN-a and OPN-b are mainly expressed in invasive HCC, while OPN-c is mainly expressed in non-invasive HCC [21]. In gastric cancer, OPN-b is associated with the survival of cancer cells, while OPN-c primarily stimulates the metastatic activity of cancer cells [22]. In addition, OPN-a and OPN-c can promote the invasion ability of glioma cells, while OPN-b has no effect on the invasion ability of glioma cells [13].

Receptors of OPN. OPN contains two integrin-binding domains: the RGD sequence and the SVVYGLR sequence, which transmit signals to the intracellular by binding to a variety of integrin receptors. The RGD sequence is the classical binding domain of OPN, which mediates the binding of OPN to integrin receptors such as αvβ1, αvβ3, αvβ5, αvβ6, α5β1, α8β1, etc. When the RGD sequence is cleaved by thrombin, the SVVYGLR sequence will be exposed, and the SVVYGLR binding domain mainly binds to α9β1, α4β1, and α4β7 integrin receptors [9, 19, 23]. The CD44 receptor binding domain is located at the carboxyl end of OPN and binds mainly to various splicing variants of the CD44 receptor (CD44v3, CD44v6, and CD44v7) [19]. With the assistance of integrin receptors or CD44 receptors, OPN regulates cell proliferation, adhesion, and migration by activating multiple intracellular signaling pathways such as PI3K/AKT, MAPK, Wnt/β-catenin, and JAK/STAT [24–26]. Therefore, blocking the binding of OPN to integrin receptors and CD44 receptors may help treat OPN-mediated pathological diseases.

OPN and cancer progression: intracellular "signal traffic networks" and downstream carcinogenic molecules

As a pro-cancer molecule, OPN plays a catalytic role in the development of malignant behavior of cancer. Many studies have confirmed that OPN is involved in cancer survival, invasion, metastasis, angiogenesis, drug resistance, and immunosuppression principally by regulating the expression of VEGF, HIF-1α, EMT-related proteins, MMP-1/2/7/9, uPA, apoptosis-related proteins, and some other oncogenic molecules. In addition, activation of multiple kinases, signaling pathways, and transcription factors play important roles in the regulation of the above oncogenic molecules.

Therefore, it is crucial to understand how OPN regulates the expression of the above-mentioned carcinogenic molecules.

OPN regulates the expression of VEGF and HIF-1α. The rapid growth and proliferation of tumor cells cause the tumor microenvironment to be in a continuous state of hypoxia, and this will stimulate angiogenesis, which continues to provide nutrients, oxygen, and metastatic pathways for tumor cells, and is closely related to the occurrence of tumor growth, survival, and metastasis [27]. HIF-1α is a class of nuclear transcription factors that mediates the cellular response to hypoxia and is overexpressed in the tumor hypoxic microenvironment, associated with cancer metastasis, angiogenesis, immune escape, tumor drug resistance, and poor prognosis [28]. In the tumor hypoxic microenvironment, HIF-1α promotes angiogenesis in tumor tissues mainly by upregulating the expression of VEGF, a key downstream target gene [29]. VEGF is a cytokine with pro-angiogenic activity, and the receptors of VEGF mainly include VEGFR1, VEGFR2 (KDR), VEGFR3, and neuropilin1/2 (NRP-1/2) [27, 30]. During tumor angiogenesis, VEGF and VEGFR are overexpressed in tumor tissues, and VEGF promotes endothelial cell proliferation, migration, invasion, and increases vascular permeability mainly by binding to VEGFR2 on the endothelial cell surface and initiating intracellular network signals such as PI3K/AKT and MAPK [27, 31]. Moreover, ECM degradation is also a key component of angiogenesis, and VEGF accelerates endothelial cell invasion and angiogenesis by inducing the expression of proteases such as uPA or MMP-2/9 that degrade the ECM and basement membrane components [32]. Besides being involved in tumor angiogenesis, the VEGF/VEGFR axis is also involved in the formation of EMT and immunosuppressive tumor microenvironment [27, 32, 33].

OPN has been identified as a hypoxia-responsive gene, and in the hypoxic tumor microenvironment, hypoxia promotes OPN overexpression in cancer cells or stromal cells through an oxygen radical-dependent manner [10, 34]. In addition, OPN was directly proportional to microvessel density in tumor tissues, and knockdown of the OPN gene significantly inhibited angiogenesis, suggesting that OPN has an angiogenesis-inducing effect [35]. A study showed that the expressions of OPN, HIF-1α, and VEGF were significantly upregulated when breast cancer cells were exposed to hypoxic conditions while silencing of the OPN gene significantly inhibited the expression of HIF-1α and VEGF and reduced the invasive ability of breast cancer cells [36]. Therefore, the expression of HIF-1α and VEGF may be regulated by the level of OPN under the continuous hypoxic stimulation of the tumor microenvironment. A study reported that OPN/αvβ3 could induce HIF-1α expression through activating the PI3K/ILK/AKT/NF-κB pathway, and then HIF-1α would promote the expression of VEGF that would induce angiogenesis, which is one of the mechanisms by which OPN promotes breast tumor growth and resists hypoxia [10]. Chemokine receptors are associated with cancer migration and metastasis, OPN may also promote C-C chemokine receptor type 1 (CCR1) expression by activating the PI3K/AKT/HIF-1α axis, which in turn could contribute to HCC migration and lung metastasis [37]. Breast tumor kinase (BRK) is a non-receptor tyrosine kinase that is overexpressed in 86% of breast cancer patients and is associated with migration and metastasis of breast cancer cells [38]. In MDA-MB-231 breast cancer cells, OPN/αvβ3 first induced phosphorylation activation of BRK and then promoted VEGF expression via the BRK/NIK/NF-κB or BRK/ATF-4 activation pathway and the tandem activation pathway between NF-κB and ATF-4 (a member of AP-1) [39]. They also found that OPN-induced VEGF bound to NRP-1 receptors on the surface of MDA-MB-231 cells and KDR receptors on the surface of endothelial cells through autocrine, paracrine, and proximate mechanisms which promoted cancer cells' motility and angiogenesis [39]. In contrast, curcumin significantly inhibited NF-κB and ATF-4 activation and reduced OPN-induced VEGF secretion, which eliminated cancer cell motility and angiogenesis [40]. Similarly, OPN/αvβ3 also promoted VEGF expression and angiogenesis in prostate cancer PC3 cells mediated by the MEK/ERK1/2 pathway activation, which was also inhibited by curcumin [41] (Figures 1 and 2). In summary, OPN, HIF-1α, and VEGF are highly expressed in the tumor hypoxic microenvironment, and OPN promotes the expression of HIF-1α and VEGF through multiple mechanisms. HIF-1α and VEGF, as downstream oncogenic molecules of OPN, play important roles in the OPN-promoted angiogenesis, invasion, metastasis, and immunosuppression. Therefore, the combination of OPN, HIF-1α, and VEGF to assess patient prognosis or the combination of all three targeted therapies may have clinical significance, while targeted inhibition of OPN, VEGF, and HIF-1α expression may be more effective in inhibiting cancer progression.

OPN regulates the expression of EMT-related proteins. EMT is the process by which epithelial cells lose intercellular junctions and apical-basal polarity and transition to mesenchymal cells, and this transition induces epithelial cells to acquire fibroblastic properties that promote cell motility and the formation of new membrane protrusions, and this is a key event in the acquisition of migratory and invasive capacity by cancer cells of epithelial origin [24]. E-cadherin, an important adhesion molecule that maintains epithelial cell junctions and is a specific protein representing the epithelial cell phenotype, is expressed at reduced levels in EMT; similarly, N-cadherin, Vimentin, and β-catenin, which are specific proteins for the mesenchymal cell phenotype, are expressed at elevated levels in EMT [24, 42]. The EMT transcription factors (EMT-TFs) such as Snail, Twist, and Slug are key inducers of EMT development, and they are involved in EMT development by suppressing E-cadherin expression and promoting N-cadherin, Vimentin, and β-catenin expression, which in turn promote cancer metastasis and invasion [43, 44]. Besides being involved in EMT, EMT-TFs, especially Twist and Snail are also associated with

MMP-1 secretion, angiogenesis, tumor resistance, and the formation of an immunosuppressive microenvironment [30, 43–46].

It was reported that OPN could not only increase the stability of Vimentin by interacting with residues 246 and 406 in Vimentin but also upregulated N-cadherin and downregulate E-cadherin by activating the PI3K/AKT/Twist pathway, which promoted EMT associated with HCC [47, 48]. In endometrial cancer, NSCLC, and prostate cancer, OPN was found to promote the transcriptional activity of Slug and Twist possibly through the activation of the dual PI3K/AKT and ERK pathways, which in turn promoted EMT by downregulating E-cadherin expression and upregulating N-cadherin and β-catenin [24, 49, 50]. In the hypoxic tumor microenvironment, pancreatic stellate cells secreted large amounts of OPN in response to hypoxic stimulation, and then OPN/αvβ3 promoted the activity of the transcription factor forkhead box protein M1 (FOXM1) by activating the AKT and ERK pathways in pancreatic cancer cells in a paracrine manner, and then FOXM1 induced EMT by inhibiting the expression of E-cadherin and promoting the expression of N-cadherin, Vimentin, and Snail [34] (Figures 1 and 2). It is thus clear that OPN is a causative agent of EMT formation, and OPN alters molecules associated with EMT development mainly through the activation of PI3K/AKT and MAPK signaling pathways. Hence, we conjecture that OPN and EMT-related molecules could serve as synergistic prognostic biomarkers and therapeutic targets for cancer.

OPN regulates the expression of MMP-1/2/7/9. MMPs are major ECM protein hydrolases involved in the regulation and remodeling of the ECM, capable of degrading almost all protein components of the ECM and playing a key role in embryonic development, tissue remodeling, inflammation, cancer, and angiogenesis [51]. Studies have confirmed that MMPs are abundantly expressed during carcinogenesis and disrupt the histological barrier that prevents tumor cell invasion, which is an important cause of cancer infiltration and metastasis [51]. Interestingly, MMPs are not only involved in tumor cell metastasis and angiogenesis through degradation of ECM and basement membrane, but they are also involved in cancer progression through inhibiting apoptosis, promoting cell cycle progression, and EMT [52–55].

It was demonstrated that the expression of MMP-1/2/7/9 may all be regulated by OPN. Recently, a study reported that OPN promoted MMP-1 expression through the activation of PI3K/AKT and Src/MEK/ERK1/2 pathways, which led to metastasis in lung cancer [14]. In HCC, OPN/αvβ3 promoted MMP-2 expression through the activation of the PI3K/AKT/SDF-1/CXCR4 signaling axis [56]. *In vitro* experiments confirmed that the combination of OPN-a and OPN-c with αvβ3 could activate the intracellular PI3K/AKT/IKK/IκBα/NF-κB pathway, and significantly enhanced the activity of MMP-2 and MMP-9 for promoting the invasive ability of glioma cells, while OPN-small interfering RNA (siRNA), anti-αvβ3 antibody, and PI3K inhibitor effectively blocked this event [13]. Glycogen synthase kinase 3-beta (GSK-3β) is a conserved serine/threonine protein kinase in eukaryotes, which is closely related to tumor growth, proliferation, apoptosis, migration, and other processes [57]. This research has demonstrated that GSK-3β has ubiquitinated degradation of β-catenin protein, which is a key mechanism for GSK-3β to inhibit the Wnt/β-catenin pathway [58]. However, GSK-3β activity is inhibited in response to phosphorylation stimulation by AKT, suggesting that PI3K/AKT can indirectly activate the Wnt/β-catenin pathway through the inactivation of GSK-3β [58, 59]. In prostate cancer, OPN/αvβ3 was shown to induce the activation of the AKT/GSK-3β/β-catenin axis through PI3K or ILK, resulting in the accumulation of β-catenin in the nucleus and enhancing the transcriptional activity of T-cell factor/lymphoid enhancing factor, promoting the increase of transcriptional and translational levels of MMP-7 and CD44, which is one of the mechanisms for the OPN to promote the progression of prostate cancer [7]. Nuclear factor inducing kinase (NIK) is a member of the MAPKKK family, whose main function is to phosphorylate IKK directly or indirectly, leading to phosphorylation and degradation of IκB, which then activates NF-κB [60]. In a study on malignant melanoma, OPN/αvβ3 was found to promote transactivation of AP-1 through activation of the NIK/ERK1/2 and MEKK1/JNK1 pathways, respectively, which in turn led to high expression of MMP-9, showing that NIK is also involved in the nuclear translocation process of AP-1 [61]. Interestingly, sustained activation of MEKK1-dependent JNK1 partially suppressed ERK1/2 activity, and in conclusion, OPN promoted melanoma growth and lung metastasis via NIK or MEKK1-dependent MMP-9 expression pathways [61]. Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase that acts as a bridge between integrin proteins and the activation of intracellular signaling pathways such as PI3K/AKT and MAPK and is involved in the adhesion, proliferation, and apoptosis of cancer cells [62]. Reportedly, OPN/αvβ3 increased the phosphorylation of FAK at tyrosine position 397, which was shown to be the active site of FAK, and then FAK induced the activation of IKK/IκB/NF-κB through the activation of both PI3K/AKT and MEK/ERK pathways, leading to the upregulation of MMP-9 levels and promoting the invasive ability of cancer cells [63, 64] (Figures 1 and 2).

OPN regulates the expression of uPA. uPA, a member of the serine protease family, is an extracellular protein hydrolase whose binding to the uPA-receptor (uPAR) produces a variety of biological effects that are closely associated with cancer progression [65]. First, uPA/uPAR complex can activate fibrinogen into fibrinolytic enzymes, which not only degrade ECM proteins (IV collagen, fibronectin, etc.) directly, but also indirectly by activating various MMP members, and this can lead to invasion, metastasis, and angiogenesis of cancer cells [65, 66]. Interestingly, besides

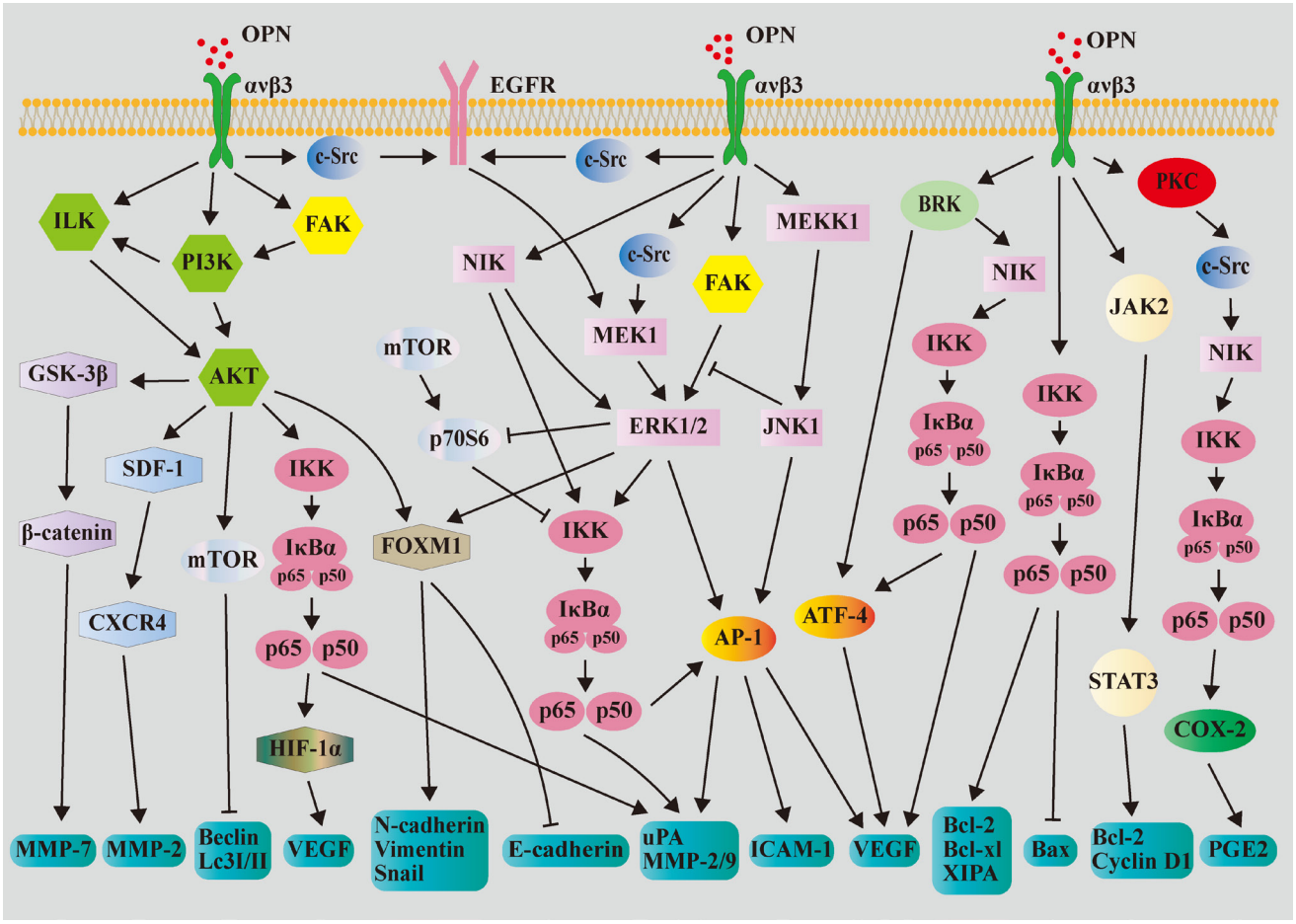

Figure 1. Mechanism of regulation of downstream oncogenic molecule expression after OPN binding to αvβ3 receptor. OPN/αvβ3 promotes MMP-7 expression by activating the PI3K/ILK/AKT/GSK-3β/β-catenin axis, leading to prostate cancer progression. OPN/αvβ3 promotes MMP-2 expression by activating the PI3K/AKT/SDF-1/CXCR4 signaling axis, leading to HCC progression. OPN/αvβ3 inhibits the expression of autophagy proteins such as LC3I/II and Beclin1 by activating the PI3K/AKT/mTOR pathway, thus reducing apoptosis in breast cancer cells. OPN/αvβ3 promotes VEGF expression by activating the PI3K/ILK/AKT/NF-κB/HIF-1α axis, inducing breast tumor angiogenesis and resistance to hypoxia. OPN/αvβ3 induces NF-κB activation by activating FAK/PI3K/AKT and FAK/MEK/ERK, thus promoting the expression of MMP-9 and enhancing cancer cell invasion. OPN/αvβ3 promotes the expression of MMP-2, MMP-9, and uPA by activating the PI3K/AKT/NF-κB axis, thus enhancing the invasive ability of glioma and breast cancer cells. OPN/αvβ3 suppresses the expression of E-cadherin and promotes the expression of N-cadherin, Vimentin, and Snail by activating the AKT/ERK/FOXM1 axis, thus promoting pancreatic carcinogenesis EMT. OPN/αvβ3 activates the MEK1/ERK1/2/AP-1 pathway by activating c-Src-mediated EGFR-dependent and non-dependent pathways, thus promoting the secretion of uPA and MMP-1, and enhancing the invasive and metastatic ability of breast cancer cells. The mTOR/p70S6 kinase inhibits the NF-κB activity, while OPN/αvβ3 inhibits mTOR/p70S6 kinase activity by activating the MEK/ERK pathway, which leads to NF-κB-dependent activation of AP-1, thus promoting the expression of ICAM-1 in breast cancer cells. OPN/αvβ3 promotes VEGF expression by activating the MEK/ERK1/2, BRK/NIK/NF-κB, and BRK/ATF-4 axes, thereby increasing cancer angiogenesis. OPN/αvβ3 promotes MMP-9 expression by activating NIK/ERK1/2/AP-1 and MEKK1/JNK1/AP-1, respectively, leading to melanoma growth and lung metastasis (MEKK1/JNK1 partially inhibits the activity of NIK/ERK1/2). OPN/αvβ3 promotes the expression of uPA and MMP-9 by activating NIK/NF-κB or NIK/MEK1/ERK1/2/NF-κB, thus enhancing the invasion of melanoma cells. OPN/αvβ3 induces COX-2-dependent PGE2 expression by activating the PKC/c-Src/NIK/NF-κB pathway, thus promoting prostate cancer invasion and angiogenesis. OPN/αvβ3 promotes the expression of Bcl2 and CyclinD1 by activating the JAK2/STAT3 pathway, thereby enhancing the anti-apoptotic and proliferative capacity of breast cancer cells. OPN/αvβ3 upregulates the expression of Bcl-2, Bcl-xl, and XIAP and downregulates the expression of Bax by activating NF-κB, thus inhibiting apoptosis and promoting the growth of HCC.

degrading the ECM, uPA also participates in the formation of EMT and angiogenesis [59, 67, 68].

Several studies have confirmed that OPN promotes high expression of uPA in a variety of cancers. The use of antibodies against uPA and uPAR was reported to significantly inhibit the OPN-mediated increase in mammary epithelial invasiveness [66]. In another study, Chen et al. used cDNA microarray technology to detect the genes most preferentially regulated by OPN, and found that HCC cells transfected with OPN expressed significantly higher levels of MMP-2 and uPA mRNA, while the change in MMP-9 was not significant [69]. Both studies suggest that the enhancement of cancer cell invasion by OPN is associated with the promotion of uPA secretion. OPN/αvβ3 was reported to first

induce phosphorylation activation of NIK, which could either directly activate IKK/IκBα/NF-κB or indirectly activate IKK/IκBα/NF-κB depending on the activation of MEK1/ERK1/2 pathway, ultimately promoting mRNA expression of uPA and MMP-9 through the enhanced transcriptional activity of p50/p65, thereby enhancing the motility and growth of melanoma cells [60]. Reportedly, OPN/αvβ3 also mediated the activation of c-Src kinase, c-Src could activate the MEK1/ERK1/2/AP-1 pathway through epidermal growth factor receptor (EGFR)-dependent and non-dependent activation, and then AP-1 entered the nucleus and promoted the secretion of uPA and MMP-1, which led to increased invasion and metastatic ability of breast cancer cells [65]. Furthermore, in highly invasive MDA-MB-231 breast cancer cells, OPN/αvβ3 promoted uPA secretion through the activation of PI3K/AKT/IKK/IκBα/NF-κB pathway, ultimately promoting the motility and invasive ability of breast cancer cells, whereas the use of PI3K, AKT, and NF-κB inhibitors significantly inhibited the above effects [15] (Figures 1 and 2).

OPN regulates the expression of apoptosis proteins. As important regulatory proteins of the apoptotic pathway, anti-apoptotic and pro-apoptotic proteins strictly regulate the process of apoptosis. Common anti-apoptotic proteins include Bcl-2, Bcl-xl, Mcl-1, and XIAP, while Bax and Bad are common pro-apoptotic proteins [70]. Under physiological conditions, the ratio of anti-apoptotic and pro-apoptotic

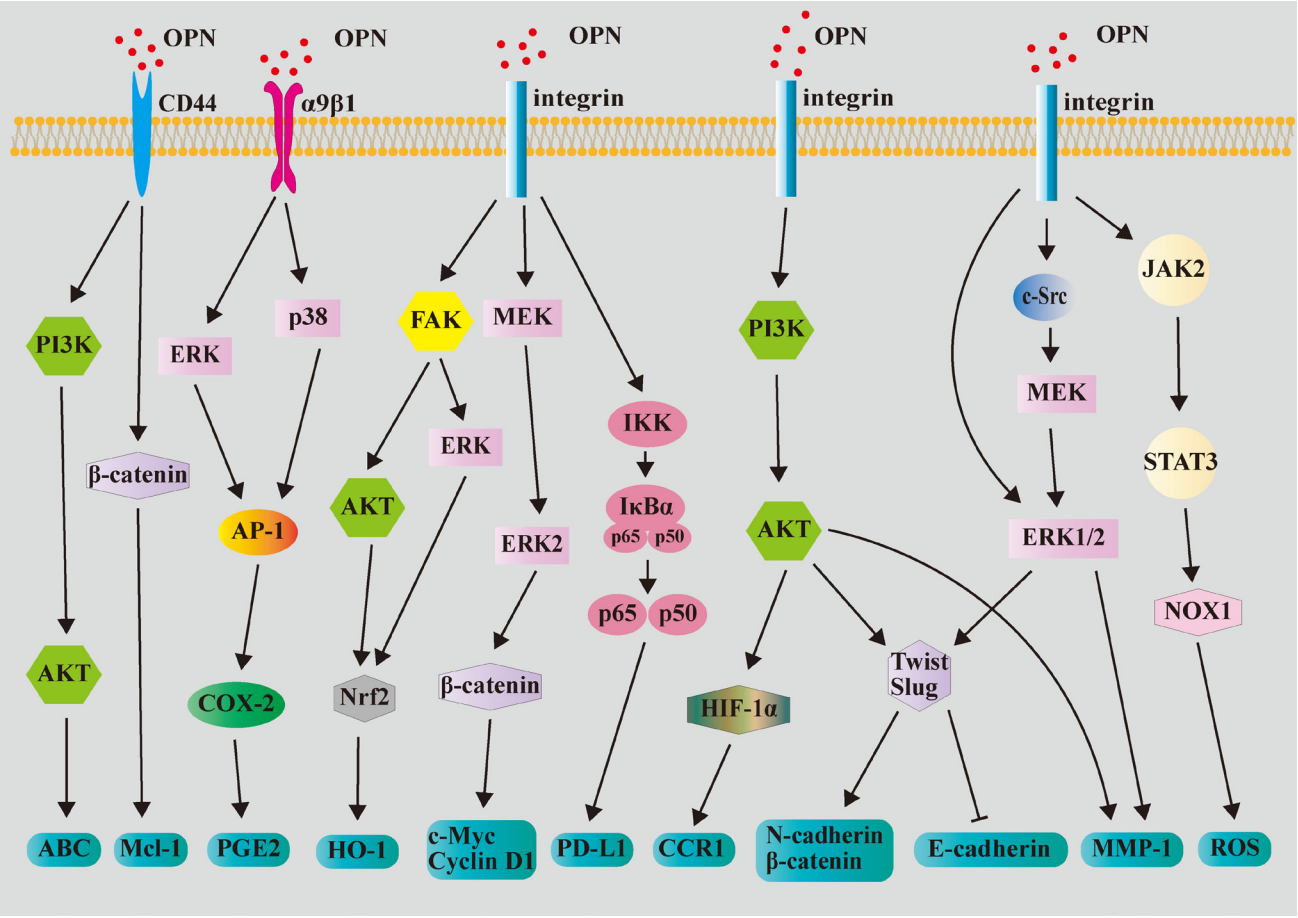

Figure 2. Mechanisms by which OPN regulates the expression of downstream oncogenic molecules after binding to other receptors. OPN/CD44 enhances ABC transporter protein activity by activating PI3K/AKT, thus inducing cisplatin resistance in ovarian cancer cells. OPN/CD44 upregulates the expression of the anti-apoptotic protein Mcl-1 by activating β-catenin, thus resisting imatinib-induced apoptosis in gastrointestinal mesenchymal tumor cells *in vitro*. OPN promotes MMP-1 expression by activating the PI3K/AKT and Src/MEK/ERK1/2 pathways, leading to metastasis in lung cancer. OPN promotes CCR1 expression by activating the PI3K/AKT/HIF-1α axis, thereby promoting HCC migration and lung metastasis. OPN promotes the transcriptional activity of Slug and Twist by activating the PI3K/AKT and ERK pathways, which in turn promotes EMT by downregulating E-cadherin expression and upregulating N-cadherin and β-catenin. OPN/NF-κB leads to the growth of NSCLC by promoting the expression of PD-L1. OPN/α9β1 leads to COX-2-mediated PEG2 secretion by activating ERK- and p38-mediated AP-1 nuclear translocation activity, ultimately promoting melanoma cell growth and angiogenesis. OPN upregulates the expression of Cyclin D1 and c-Myc by activating the MEK/ERK2/β-catenin axis, which in turn promotes cell cycle progression and proliferation of intrahepatic cholangiocarcinoma cells. OPN induces the activation of Nrf2/HO-1 by activating FAK/PI3K/AKT and FAK/ERK pathways to protect cancer cells from oxidative stress damage and enhance cancer cell migration. OPN induces ROS secretion by activating JAK2/STAT3/NOX1 to promote the proliferation and migration of HCC.

proteins is in a stable dynamic balance, strictly regulating the downstream caspases kinase cascade reaction, however, cancer cells exhibit apoptosis resistance in cancer development, which is mainly caused by the increase of anti-apoptotic proteins and decrease of pro-apoptotic proteins [71].

It was confirmed that OPN could participate in inhibiting the apoptotic process by activating anti-apoptotic signals and inhibiting pro-apoptotic signals and enhance the apoptosis resistance and survival of cancer cells. In small cell lung cancer studies, OPN could inhibit caspase-3 and caspase-9-dependent apoptosis by promoting Bcl-2 protein expression, while enhancing chemoresistance to cisplatin in lung cancer SBC-3 cell lines [72]. In breast cancer studies, OPN/αvβ3 promoted the expression of Bcl2 and the cell cycle factor CyclinD1 through the activation of the JAK2/STAT3 pathway, which enhanced the apoptosis resistance and proliferation of cancer cells [26]. In addition, Hsu et al. found that OPN/CD44 probably counteracted imatinib-induced apoptosis in gastrointestinal mesenchymal tumor cells *in vitro* by activating β-catenin-mediated upregulation of the anti-apoptotic protein Mcl-1 [73]. When the OPN gene was structurally silenced by short hairpin RNA (shRNA), the activity of the OPN/αvβ3/NF-κB pathway was significantly decreased and HCC exhibited downregulation of expression of anti-apoptotic proteins Bcl-2, Bcl-xl, and XIAP and upregulation of expression of pro-apoptotic protein Bax, ultimately leading to increased apoptosis and growth restriction of HCC [16] (Figures 1 and 2). In summary, OPN confers apoptosis-resistant properties to cancer cells mainly by promoting the expression of Bcl-2, Bcl-xl, Mcl-1, and XIAP and inhibiting the expression of Bax.

OPN regulates the expression of other oncogenic molecules. Programmed cell death-1 (PD-1) and programmed cell death ligand 1 (PD-L1) are immune checkpoint suppressor molecules, which are one of the main causes of immune escape from tumor cells [74]. New evidence suggested that tumor-associated macrophage-derived OPN possibly promoted PD-L1 expression in NSCLC by activating the NF-κB pathway, which resulted in tumor growth [74]. In addition, ATP-binding cassette (ABC) transporter protein-mediated drug efflux is a key protein for chemical drug resistance in tumor cells. In ovarian cancer studies, OPN secreted by cancer-associated mesothelial cells was found to activate the PI3K/AKT pathway through the CD44 receptor, which in turn enhanced the activity of ABC transporter protein, leading to drug efflux and inducing cisplatin resistance in ovarian cancer cells [75]. Cyclooxygenase-2 (COX-2) has been shown to be overexpressed in cancer and is closely associated with tumor cell proliferation, invasion, and angiogenesis. Jain et al. found that OPN/αvβ3 induced COX-2-dependent prostaglandin E2 (PGE2) expression by activating the PKC/c-Src/NIK/IKK/IκBα/NF-κB pathway and that PGE2 binding to tumor cell or endothelial cell receptors promoted prostate cancer growth, invasion, and angiogenesis, while the nonsteroidal anti-inflammatory drug celecoxib significantly inhibited OPN-induced cancer progression [76]. Similar research also found that OPN activated macrophage surface α9β1 receptors in an autocrine manner, which in turn activated intracellular ERK and p38-mediated nuclear translocation activity of AP-1, leading to COX-2-mediated secretion of PEG2 and ultimately promoting melanoma cell growth and angiogenesis [77]. mTOR is a serine/threonine protein kinase that is mainly activated by the PI3K/AKT pathway, it is also a key regulator of autophagy and has an inhibitory effect on the autophagic process [78]. When the OPN gene was specifically knocked down, the αvβ3-mediated PI3K/AKT/mTOR pathway was inactivated in MDA-MB-231 cells, which led to the upregulation of autophagy proteins such as LC3I/II and Beclin1 and activated the autophagy pathway, resulting in increased apoptosis and inhibition of migration, suggesting that the activation of mTOR is involved in promoting the oncogenic process of OPN process [79]. Intercellular adhesion molecule-1 (ICAM-1) belongs to the immunoglobulin superfamily of adhesion molecules, which induces cell motility and migration, and is closely related to angiogenesis and cancer metastasis [80]. It was reported that OPN could selectively induce p70S6 kinase phosphorylation at Thr-421/Ser-424 and inhibit p70S6 kinase activity by activating the MEK/ERK pathway, which would lead to NF-κB-dependent transactivation of AP-1 and promote ICAM-1 expression in breast cancer cells [81]. Whereas, mTOR overexpression inhibited the above OPN-induced ICAM-1 secretion by inducing p70S6 kinase phosphorylation at the Ser-371 site and activating p70S6 kinase activity, suggesting that mTOR activation is in turn involved in inhibiting the oncogenic process of OPN [81]. In addition, it was also possible that OPN induced Ser675 phosphorylation and nuclear accumulation of β-catenin protein by activating the MEK/ERK2 pathway, which in turn activated the Wnt/β-catenin pathway and upregulated the expression of downstream target genes CyclinD1 and c-Myc to promote cell cycle progression and proliferation of intrahepatic cholangiocarcinoma cells [82]. The Nrf2/HO-1 axis is a key signaling pathway against oxidative stress, and recombinant human OPN promoted the accumulation of Nrf2 in the nucleus by activating the FAK/PI3K/AKT and FAK/ERK pathways in malignant glioma cells, and the binding of Nrf2 to DNA further promoted HO-1 expression, protecting cancer cells from oxidative stress damage and enhancing the migration of cancer cells [83]. Overexpression or dramatic elevation of reactive oxygen species (ROS) as a damaging factor that induces apoptosis in cancer cells. However, the cellular experiment found that OPN could increase the expression of NADPH oxidase 1 (NOX1) by activating the JAK2/STAT3 pathway, and NOX1 further significantly promoted the proliferation and migration of HCC by inducing the secretion of ROS [84]. Based on the result of this experiment, the authors concluded that a moderate increase in ROS levels could also promote cancer progression (Figures 1 and 2).

Prognostic value of OPN in common cancers

The study of cancer biomarkers has long been a focus in the field of cancer research, and researchers have found that biomarkers play an important role in the diagnosis or differential diagnosis of cancer, monitoring cancer progression, as well as assessing the risk of recurrence after treatment. After reviewing the relevant literature, we observed that the overexpression of OPN in circulation or tissues is a predictable biomarker for breast cancer, NSCLC, colorectal cancer, prostate cancer, gastric cancer, and HCC, and it can be used to assess the histological grade, clinical stage, tumor progression, treatment responsiveness, postoperative recurrence risk, overall survival (OS), and disease-free survival (DFS) of these cancers [85–90]. Here, we summarized some important studies. In addition, it was found that some biomarkers may be poor in cancer-independent prognosis, while the combination of different biomarkers may improve the specificity and sensitivity of diagnosis. To improve the value of OPN in cancer prognosis, we reviewed the synergistic prognostic value of OPN in combination with downstream oncogenic molecules in cancer, considering that OPN regulates the expression of multiple oncogenic molecules.

Prognostic value of OPN in breast cancer. Female breast cancer has surpassed lung cancer as the most prevalent cancer worldwide (11.7%) and is the fifth leading cause of cancer-related deaths (6.9%) [1]. Many previous and current studies have confirmed that high levels of OPN in circulating or cancerous tissues can be used as an independent predictive biomarker for breast cancer. Early studies found that in patients with metastatic breast cancer, plasma OPN levels increased progressively with disease progression and were associated with lower survival rates, and they ventured to speculate that continuous monitoring of plasma OPN might be useful in assessing patients' next steps in treatment [91]. A meta-analysis showed that overexpression of OPN was positively associated with lymph node metastasis, predicting significantly lower OS and DFS in patients [85]. Triple-negative breast cancer cells overexpressing OPN appeared to be more sensitive to the growth inhibition produced by the EGFR inhibitor erlotinib compared to controls, which was due to the OPN-mediated kinase pathway could promote EGFR expression, this indicates that overexpression of OPN may serve as a potential biologic factor to assess the efficacy of EGFR inhibitors in triple-negative breast cancer [92]. In a recent study of breast cancer patients treated with tamoxifen for recurrence or non-recurrence, higher levels of SSP1 mRNA in the primary tumor were found to be associated with the risk of recurrence, whereas OPN protein expression did not predict the risk of recurrence [93]. OPN-c is not expressed or expressed at low levels in normal breast tissue but is overexpressed in breast cancer, and high levels of OPN-c may be a more reliable prognostic molecule for low patient survival compared to OPN [94]. OPN-c was particularly highly expressed in HER2 overexpression or triple-negative/basal-like subtypes of breast cancer with a highly aggressive phenotype and was positively associated with early mortality, high aggressiveness, and risk of recurrence in patients [95, 96]. In addition, high levels of OPN-c may also be a risk prognostic factor for the succession of precancerous breast lesions such as mammary hyperplasia and papilloma to highly invasive breast cancer [97]. Therefore, OPN in blood or tissue, especially OPN-c, can be used as a prognostic biomarker for female breast cancer patients.

Prognostic value of OPN in NSCLC. Lung cancer is the second most common cancer worldwide (11.4%) and the leading cause of death among cancer patients (18%) [1]. In the OPN and lung cancer prognosis study, researchers have focused all their attention on NSCLC. In 2014, a meta-analysis assessed the value of tissue OPN levels in NSCLC patients studied [86]. The authors included 11 studies that met the criteria, including 1,536 NSCLC tumor tissues and 340 normal lung tissues, and OPN expression levels were significantly higher in NSCLC tissues compared with normal lung tissues, and overexpressed OPN was positively correlated with adverse pathology, lymph node metastasis, and tumor size, but OPN was not associated with clinical features such as degree of differentiation [86]. Another meta-analysis showed that both high plasma/serum/pleural effusion OPN concentration (PSPO) and tumor tissue OPN expression (TTO) were associated with a poor survival rate of lung cancer patients, PSPO was especially suitable for the evaluation of advanced patients [98]. Bioinformatics also confirmed that mRNA and protein expression levels of SPP1 were significantly higher in lung adenocarcinoma tissues than in normal controls, and overexpression of SPP1 was associated with males, higher N stage, higher histological grade, risk of recurrence, and lower 5-year OS but SPP1 was weakly associated with $CD4^+$T cell, macrophage, neutrophil, and dendritic cell infiltration [99]. Therefore, both OPN mRNA and protein levels may be independent prognostic factors for NSCLC.

Prognostic value of OPN in prostate cancer. Global cancer data for men in 2020 showed that prostate cancer has become the second most common cancer and the fifth leading cause of cancer death among men [1]. Reportedly, OPN overexpression was positively correlated with the malignancy of prostate cancer and predicted a shorter survival time for patients [100]. Recently, a meta-analysis showed that overexpression of OPN was positively correlated with Gleason score, TNM stage, Whitmore-Jewett stage, lymph nodes and distant metastases, which was detrimental to OS and RFS [87]. Moreover, OPN-c was the most upregulated isoform in prostate cancer tissues compared to benign prostatic hyperplasia tissues, and the sensitivity and specificity for diagnosing prostate cancer reached 90% and 100%, respectively, suggesting that OPN-c may help to differentiate the diagnosis of prostate cancer [101]. Thus, these studies suggest that OPN and OPN-c can be used to predict the prognosis of patients with prostate cancer.

Prognostic value of OPN in gastric cancer. According to Global Cancer Statistics 2020, gastric cancer has become the fifth most common malignancy (5.6%) and the fourth leading cause of death among cancer patients (7.7%) worldwide, with the incidence rate in men, equal to twice that of women [1]. Bioinformatics analysis suggested that SSP1, the gene encoding OPN, might serve as a potential predictor of prognosis and immunotherapy in patients with gastric cancer [102]. Chen et al. analyzed the serum OPN expression levels in patients with mild superficial gastritis, atrophic gastritis, and gastric cancer in a northern Chinese population [103]. They found that with the aggravation of gastric mucosal tissue lesions, serum OPN showed a stepwise increase, and serum OPN levels were significantly higher in patients with gastric cancer than in precancerous lesions, and the sensitivity and specificity of serum OPN levels for the differential diagnosis of gastric cancer and precancerous lesions reached 74.3% and 71.8%, respectively [103]. This study suggests that serum OPN levels may be useful in the risk assessment and the differential diagnosis of gastric cancer and precancerous lesion development. In addition, high levels of plasma OPN were closely associated with the occurrence of advanced stage, infiltration, metastasis, and poor prognosis in patients with gastric cancer, and could be used as an independent predictive molecule for the diagnosis and prognosis of gastric cancer [104]. A meta-analysis also revealed that the high expression of OPN was related to lymph node metastasis, depth of invasion, TNM stage, tumor size, distant metastasis, and short survival time of gastric cancer, which had better prognostic value in patients undergoing surgery [88]. Polymorphisms in the promoter of the OPN gene were also associated with the risk of metastasis and death in gastric cancer [105]. The authors found that there were C/C, C/T, and T/T variant genes in the nt-443 region of the OPN promoter, and significantly more stage IV patients with C/C-type genes than stage I patients, and the survival rate of patients with C/C-type genes was also significantly lower than that of patients with the other two types [105]. They speculated that polymorphic variants in the nt-443 region of the OPN promoter (especially C/C-type genes) might increase the risk of metastasis and death in gastric cancer patients [105]. Also, Tang et al. demonstrated that the expression levels of OPN-a, OPN-b, and OPN-c were significantly higher in gastric cancer tissues than in normal tissues and that high expression of OPN-b and OPN-c was associated with clinicopathological features such as deeper invasion, lymph node metastasis, and clinical staging, whereas OPN-a was not associated with clinicopathological features [22]. In contrast, a recent study found that high levels of OPN-a and OPN-b predicted shorter OS and DFS, whereas low levels of OPN-c were instead associated with poor prognosis, and in addition, increased expression of OPN-a alone was associated with increased TNM staging [106]. The above study illustrates that the three splice variants of OPN have unique prognostic value in gastric cancer. However, their role in the prognosis of gastric cancer is still controversial, and the reasons for these different results may be due to differences in gastric cancer cell lines or tissues, and further studies are needed to confirm. In conclusion, OPN may be of research value in the early differential diagnosis, malignant behavior, survival rate, and prognosis of gastric cancer.

Prognostic value of OPN in colorectal cancer. Colorectal cancer is the third most prevalent cancer (10.0%) and the second most prevalent cancer-related mortality (9.4%) malignancy worldwide [1]. Despite some progress in early diagnosis and clinical treatment, the current status of patient prognosis is still not promising. Therefore, there is a certain need to search for more biomolecules that can predict the prognosis of patients. Thus, we focus our attention on studies on the prognostic value of OPN in patients with colorectal cancer, which unfortunately may have several inconsistent findings. Wang et al. found that high OPN mRNA expression levels were significantly and positively correlated with lymph node metastasis, lymphatic or venous infiltration, and TNM stage, and were independent prognostic factors for reduced OS and DFS in patients with colorectal cancer [107]. However, Li et al. concluded that OPN protein overexpression was not associated with tumor infiltration depth and TNM stage, but significantly associated with lymph node metastasis and Dukes stage [108]. A study on colorectal cancer patients in China showed that polymorphisms in the OPN genes rs9138 and rs1126616 might also be associated with the risk of colorectal cancer [109]. They found a significantly higher frequency of expression of the AA and AC genotypes of rs9138 and the CC and CT genotypes of rs1126616 and confirmed that patients carrying the rs9138A and rs1126616C genes were associated with an increased risk of colorectal cancer [109]. Recently, a meta-analysis further confirmed that OPN overexpression was significantly associated with high tumor grade, lymph node metastasis, and distant tumor metastasis, as well as with shorter 2-, 3-, and 5-year OS [89]. The above studies suggest that OPN can be used as an unfavorable prognostic biomarker and potential therapeutic target for colorectal cancer patients. In contrast, Assidi et al. found that SPP1 expression in the cytoplasm and nucleus of colorectal cancer patients in Saudi Arabia was significantly higher than SPP1 expression in colon adenomas and normal colon mucosa, but overexpressed SPP1 showed a significant negative correlation with distant metastasis, tumor invasion, tumor grade, and recurrence, and patients with SPP1 overexpression in the cytoplasm had a lower recurrence rate and better prognosis, while cytosolic SSP1 was not associated with prognosis [20]. This study presents us with cytoplasmic SPP1 overexpression as an independent favorable prognostic molecule in colorectal cancer patients, in complete contrast to previous studies, which may be related to the molecular pathology, characteristic genetic mutations or environmental alterations, and multiple isoforms or functions of SSP1 in Saudi Arabian patients, and more precise studies are needed

to further analyze the value of OPN in the prognosis of colorectal cancer patients.

Prognostic value of OPN in HCC. Primary liver cancer is the sixth most common malignancy and the third leading cause of cancer death worldwide (8.3%), with approximately 900,000 new cases reported and 830,000 deaths per year, of which HCC is the most common histologic type [1]. An early study has shown that OPN mRNA overexpression was associated with larger tumors, high-grade, advanced HCC, and was a prognostic factor for early tumor recurrence or metastasis and lower 10-year survival rates [110]. In a study of 151 patients (including 112 TNM stage I patients) who underwent hepatectomy, the overexpression of OPN protein in tissues was found to be associated with early postoperative recurrence and was an independent prognostic factor for OS and DFS in patients with TNM stage I HCC, which could help determine those individual patients who require adjuvant therapy to prevent early recurrence after surgical resection [111]. Besides, several meta-analyses showed that overexpression of OPN in tissue, serum, or plasma not only predicted poor OS and DFS in HCC patients but also was related to tumor size (>5 cm), advanced TNM stage and

Table 1. Combined predictive value of OPN synergistic downstream oncogenic molecules in cancers.

Biomarkers	Cancer type	Results/Conclusions	References
OPN+COX-2	breast cancer	Concurrent overexpression of OPN and COX-2 in patients with more aggressive HER2 subtype breast cancer is associated with poor prognosis, suggesting that the combination of OPN and COX-2 predicts high aggressiveness in breast cancer.	[119]
OPN-c+E-cadherin+β-catenin	breast cancer	OPN-c expression correlated with lymph node metastasis, advanced TNM staging, and histological grading, whereas E-cadherin and β-linked protein expression correlated with low TNM staging and histological grading.	[120]
OPN+PGE2	HCC	Serum OPN and PGE2 levels were both significantly higher in HCC patients than in controls, and they may contribute to the screening and surveillance of HCC in high-risk populations and potentially improve patient prognosis.	[121]
OPN+E-cadherin	HCC	Low expression of E-cadherin mRNA and high expression of OPN mRNA were associated with a higher likelihood of early relapse in patients with HCV-HCC.	[122]
OPN+CCR1	HCC	OPN expression was positively correlated with CCR1 expression, and patients with high OPN and high CCR1 expression had the highest tumor recurrence rates and the shortest OS. The combination of OPN and CCR1 was an independent prognostic indicator of survival and recurrence.	[37]
OPN+caspase-3	HCC	Patients with higher OPN levels and lower caspase-3 levels have a higher postoperative recurrence and poorer prognosis, and both can be used as valid predictors of recurrence after curative resection in HCC patients.	[123]
OPN+ICAM-1	HCC	HCC patients with high preoperative levels of OPN or ICAM-1 have a high recurrence rate and poor prognosis. Combined OPN+ICAM-1 assessment allows a more accurate assessment of patient recurrence and prognosis compared to OPN or ICAM-1 alone.	[124]
OPN+VEGF	NSCLC	Patients with stage I adenocarcinoma with both VEGF and OPN positive adenocarcinoma had a worse prognosis, higher postoperative recurrence rate, and higher microvascular counts compared to VEGF positive or OPN positive adenocarcinoma, and VEGF negative and OPN negative adenocarcinoma.	[125]
OPN+CD44v6+MMP-2	NSCLC	OPN, CD44v6, and MMP-2 overexpression are associated with histology, TNM staging, and lymph node metastasis. They can be used as clinical indicators to predict the progression and metastatic potential of lung squamous cell carcinoma and adenocarcinoma.	[126]
OPN+MMP-7	NSCLC	Protein and mRNA of OPN and MMP-7 are overexpressed in cancer tissues, and both are associated with TNM stage and lymph node metastasis, which are independent risk factors for a poor prognosis in NSCLC patients.	[127]
OPN+PD-L1	NSCLC	There was a positive correlation between OPN and PD-L1 expression, with high levels of both OPN and PD-L1 predicting significantly lower 5-, 8-, and 10-year OS and DFS for patients.	[74]
OPN+COX-2+VEGF	gastric cancer	OPN, COX-2, and VEGF overexpression and co-expression in gastric cancer tissues were significantly correlated with TNM stage, lymph node metastasis, distant metastasis, and microvascular density but not with patient prognosis.	[128]
OPN+E-cadherin+β-catenin	gastric cancer	RFS and OS were significantly worse in patients with OPN overexpression and in patients with abnormal E-cadherin and β-catenin expression, but E-cadherin and β-catenin were not independent prognostic factors, and OPN overexpression was a valuable independent predictor of postoperative tumor recurrence and survival in patients.	[129]
OPN+nuclear β-catenin	colorectal cancer	There was a high correlation between OPN overexpression and abnormal nuclear β-catenin expression and lymph node metastasis, depth of infiltration, TNM stage, Dukes stage, and poor prognosis, and both are unfavorable prognostic factors for colorectal cancer patients.	[130]

tumor vascular invasion, indicating that OPN has the potential to predict HCC invasion and metastasis [90, 112, 113]. However, another study believed that the plasma OPN level was directly related to the number of tumors, but not to the size of tumors [114]. In addition, overexpression of OPN protein was detected in 72 patients with hepatitis B virus-associated HCC hepatectomy, and high levels of OPN were associated with the development of envelope infiltration, portal vein infiltration, and lymph node infiltration, and patients had significantly shorter mean OS and DFS [115]. It was reported that the overexpression of OPN was positively correlated with alpha-fetoprotein (AFP), and the sensitivity of OPN was higher than that of AFP [116, 117]. Importantly, the combination of OPN + AFP seemed to improve the diagnostic accuracy of HCC [117, 118]. The above studies illustrate that overexpression of tissue OPN protein can be an independent prognostic factor and a potential therapeutic target for patients with HCC.

Conclusions and outlook

It is well established that OPN is overexpressed in multi-system cancers. In this article, we basically reveal the mechanism by that OPN promotes cancer progression, which involves the activation of certain key kinases, signaling pathways, and transcription factors. Those factors form an intracellular "signaling traffic network" and regulate the expression of downstream oncogenic molecules (VEGF, HIF-1α, MMP-1/2/7/9, uPA, PD-L1, COX-2, PGE2, etc.), and alterations in the levels of these molecules are key aspects for OPN to promote cancer invasion, metastasis, angiogenesis, drug resistance, and immunosuppression. This suggests that OPN and its downstream oncogenic molecules may serve as predictive biomarkers for cancer (Table 1). In the study of OPN and cancer prognosis, the authors mainly used two reliable techniques to detect OPN protein expression: immunohistochemical techniques to detect OPN expression in tissues and ELISA to detect OPN expression in blood. We find high levels of OPN in tissue or blood as a poor independent prognostic biomarker that positively correlates with cancer metastasis, advanced stage, recurrence, shorter OS and DFS, as well as the combined predictive value of OPN with downstream oncogenic molecules in cancer. Although the above studies are sufficient to confirm the independent prognostic value of OPN in these cancers, the differences in their study data sizes and study methods may cause some errors. In the future, we should establish a unified study protocol to further validate the value of OPN expression levels in cancer prognosis on the basis of sufficiently large clinical data and to obtain standard reference values for OPN in tissues or blood by comparing them with the expression levels of OPN in normal tissues or blood samples. Also, we need to further focus on the value of OPN in combination with other reliable biomarkers in the assessment of cancer progression and prognosis.

In the terms of treatment, there have been relevant reviews summarizing therapies targeting OPN, which include RNA-specific silencing techniques (siRNA, shRNA), specific antibodies (anti-OPN, anti-integrin receptor, anti-CD44 receptor), kinase or pathway inhibitors, and herbal components (curcumin, andrographolide) [8, 131]. However, these approaches are still in preclinical studies and lack the support of safe clinical study data. Currently, the role of combination therapeutics in targeted cancer therapy is receiving increasing attention. Based on the fact that the oncogenic effect of OPN correlates with the expression of downstream oncogenic molecules, we may try to combine anti-OPN therapies with anti-VEGF antibodies, anti-PD-L1 antibodies, MMP inhibitors, COX-2 inhibitors, etc. Because these antibodies or inhibitors hαve already showed better therapeutic effects in clinical studies, they may be able to improve the therapeutic effect of targeted inhibition of OPN. However, little research has been reported on the combination therapy of OPN, which is a breakthrough point worthy of further study.

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