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## Osteopontin as potential biomarker and therapeutic target in gastric and liver cancers

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### Abstract

Gastric cancer and liver cancer are among the most common malignancies and the leading causes of death worldwide, due to late detection and high recurrence rates. Today, these cancers have a heavy socioeconomic burden, for which a full understanding of their pathophysiological features is warranted to search for promising biomarkers and therapeutic targets. Osteopontin (OPN) is overexpressed in most patients with gastric and liver cancers. Over the past decade, emerging evidence has revealed a correlation of OPN level and clinicopathological features and prognosis in gastric and liver cancers, indicating its potential as an independent prognostic indicator in such patients. Functional studies have verified the potential of OPN knockdown as a therapeutic approach *in vitro* and *in vivo*. Furthermore, OPN mediates multifaceted roles in the interaction be-

tween cancer cells and the tumor microenvironment, in which many details need further exploration. OPN signaling results in various functions, including prevention of apoptosis, modulation of angiogenesis, malfunction of tumor-associated macrophages, degradation of extracellular matrix, activation of phosphoinositide 3-kinase-Akt and nuclear factor- $\kappa$ B pathways, which lead to tumor formation and progression, particularly in gastric and liver cancers. This editorial aims to review recent findings on alteration in OPN expression and its clinicopathological associations with tumor progression, its potential as a therapeutic target, and putative mechanisms in gastric and liver cancers. Better understanding of the implications of OPN in tumorigenesis might facilitate development of therapeutic regimens to benefit patients with these deadly malignancies.

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**Key words:** Osteopontin; Gastrointestinal cancer; Metastasis; Prognosis; Biomarker

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### INTRODUCTION

Gastric and liver cancers are among the most common malignancies and leading causes of death worldwide,

which carries a heavy socioeconomic burden. Until now, surgical resection has remained the frontline treatment for patients with early stage gastric and liver cancers. Nevertheless, the majority of such patients have poor prognosis due to high rates of tumor recurrence as well as lymph node (LN) and systemic metastases. Therefore, a full understanding of gastric and liver cancers is crucial to develop useful prognostic markers and therapeutic targets. During the past decade, emerging evidence has refined the value of osteopontin (OPN) as a candidate biomarker and target for cancer therapy<sup>[1]</sup>. OPN is a secretory extracellular matrix (ECM) protein that is involved in a series of physiological and pathophysiological processes including but not limited to cell attachment, migration, invasion, proliferation, tissue remodeling, bone formation and even inflammation<sup>[1-4]</sup>. OPN is frequently overexpressed in human cancers and contributes to tumor formation and progression<sup>[5,6]</sup>. OPN belongs to the small integrin binding ligand N-linked glycoprotein family, which consists of members serving as markers of early cancer progression, due to their capabilities in modulating the activity of matrix metalloproteinases (MMPs)<sup>[7]</sup>. OPN participates in the interactions between cancer cells and tumor stroma, which plays a pivotal role in malignant cancer phenotype. A more thorough understanding of the functional role of OPN in the tumor microenvironment is warranted. There have been many reports on OPN and gastric and liver cancers, therefore, this review aims to summarize recent findings on clinical implications of OPN, its potential as a therapeutic target, and its related mechanisms in these two types of cancer. Further understanding on the role of OPN in gastric and liver cancers may facilitate development of therapeutic strategies in such patients.

## OPN GENE AND PROTEIN STRUCTURE

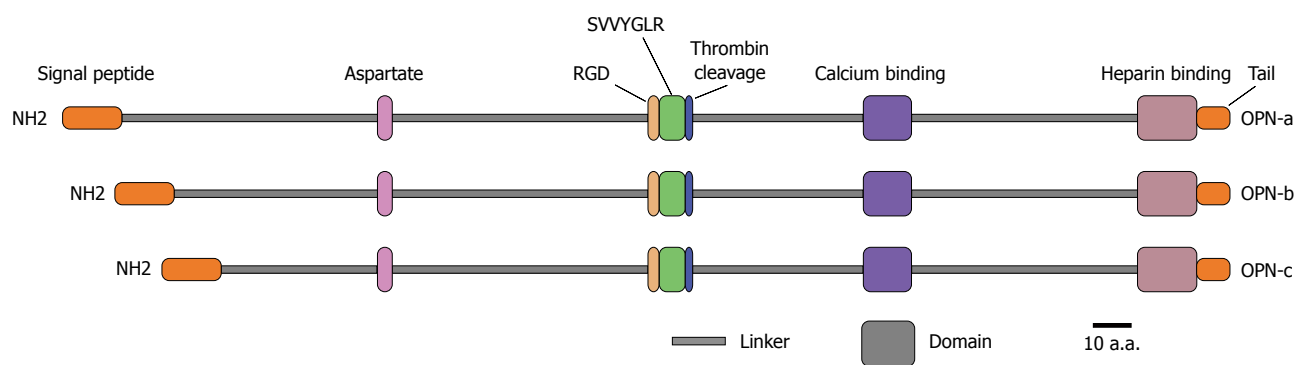
OPN is a matrix glycoprotein secreted by a variety of cell types including osteoclasts, endothelial cells, epithelial cells, and activated immune cells such as macrophages and T cells<sup>[8]</sup>. It is also known as bone sialoprotein I, early T lymphocyte activation 1 and secreted phosphoprotein 1<sup>[9-11]</sup>. Human *OPN* gene is located on chromosome 4q21-q25, spans approximately 11 kb, and consists of seven exons encoding the OPN protein with 314 amino acid residues<sup>[12]</sup>. It contains several highly conserved structural elements, including arginine-glycine-aspartate and Ser-Val-Val-Tyr-Gly-Leu-Arg domains for integrin binding, a calcium binding site and a heparin binding domain for CD44 receptor binding<sup>[13]</sup> (Figure 1). Alternative splicing produces three OPN isoforms, OPN-a, OPN-b and OPN-c, which probably display different expression profiles and functional heterogeneity in a tumor-specific manner<sup>[14,15]</sup>. Moreover, OPN protein is subjected to a series of post-translational modifications including serine/threonine phosphorylation, glycosylation and tyrosine sulfation, resulting in molecular variants ranging from 25 to 75 kDa<sup>[16]</sup>. These modifications are cell type specific and depend on physiological and pathophysiological factors, which likely affect both OPN structure and functions<sup>[17]</sup>.

ological factors, which likely affect both OPN structure and functions<sup>[17]</sup>.

## OPN OVEREXPRESSION AND CLINICAL VALUE IN PATIENTS WITH GASTRIC CANCER

OPN expression is significantly elevated in most gastric cancer patients at both transcriptional and translational levels<sup>[18-24]</sup>. OPN protein is overexpressed in both primary gastric cancer and metastatic lesions, mildly expressed in the epithelial cells in chronic atrophic gastritis that is a precancerous lesion for gastric cancer, and negatively in normal gastric mucosa, which indicates that OPN may play a role and serve as a potential biomarker in the formation and progression of gastric cancer<sup>[18-20]</sup>. Moreover, Wu *et al*<sup>[19]</sup> have found higher OPN plasma level in gastric cancer patients as compared with healthy individuals, suggesting that OPN plasma level may also be a biomarker for gastric cancer, and is of particular clinical interest because plasma-derived biomarkers are more convenient in clinical application than biomarkers from tissues. In gastric cancer tissues, OPN protein is diffusely located in the cytoplasm of tumor cells as well as tumor-associated macrophages (TAMs), which is in line with its implications in the interactions between cancer cells and tumor stroma.

Until now, the diagnostic and prognostic values of OPN have been implicated in gastric cancer patients. Microarray studies have identified gene signatures including OPN in gastric cancer patients<sup>[18]</sup>. OPN overexpression is significantly associated with clinicopathological parameters in gastric cancer such as low apoptotic index, high proliferative index, low grade, high stage, LN and vascular invasion, and distant metastasis<sup>[20-24]</sup>. In addition, OPN overexpression is an independent predictor of poor prognosis and tumor recurrence in patients with gastric cancer<sup>[21,22]</sup>. Dai *et al*<sup>[22]</sup> have suggested that patients with OPN-positive gastric cancer have poorer outcome than OPN-negative cases. Multivariate analysis has revealed OPN expression as an independent prognostic indicator of poor disease-free and overall survival in patients with gastric cancer, particularly for survival in cases in tumor, node, metastasis (TNM) stage II and III. The prognostic value of the marker combinations of OPN with conventional biomarkers has also been explored in gastric cancer patients. Zhang *et al*<sup>[24]</sup> have found the combination of OPN and caudal-related homeobox gene 2 (*CDX2*) as a survival predictor of advanced gastric cancer patients. OPN plasma level is commonly elevated in patients with gastric cancer, and is significantly associated with the clinicopathological features including late stage, serosal invasion, LN and vascular invasion, and liver metastasis<sup>[19]</sup>. High OPN plasma level is inversely correlated with poor prognosis in gastric cancer patients, especially in those with invasive phenotypes. Thus, elevated OPN plasma level may serve as an independent risk factor for poor survival in gastric cancer patients.



**Figure 1 Structural features of osteopontin isoforms.** Three isoforms of osteopontin (OPN), OPN-a, OPN-b and OPN-c, are known. All of them possess identical domains [aspartate domain, arginine-glycine-aspartate domain, Ser-Val-Val-Tyr-Gly-Leu-Arg (SVVYGLR) domain, thrombin cleavage domain, calcium binding domain and heparin binding domain] that are linked together with various linkers. These isoforms distinguish themselves by having a variable length of the linker between signal peptide and aspartate domain. RGD: Arginine-glycine-aspartate.

## OPN OVEREXPRESSION AND CLINICAL VALUE IN PATIENTS WITH LIVER CANCER

OPN is positive in most hepatocellular carcinoma (HCC) patients at both transcriptional and translational levels<sup>[25-35]</sup>. Yuan *et al.*<sup>[28]</sup> demonstrated OPN mRNA overexpression in 79 (51%) of 156 primary HCC patients. Kim *et al.*<sup>[35]</sup> disclosed that OPN protein was expressed in 92 (32.3%) of 285 tumors. The expressions of OPN mRNA and protein display a positive correlation<sup>[29]</sup>. In HCC, OPN is secreted by both cancer cells and TAMs, and secreted by bile duct epithelium and stellate cells, but not by normal hepatocytes or Kupffer cells, in normal liver conditions<sup>[34,35]</sup>. OPN<sup>+</sup> cancer cells are often dispersed in the periphery of cancer nodules and are adjacent to stromal cells<sup>[34,35]</sup>. In addition, OPN plasma level is also significantly elevated in HCC patients, especially in those with cirrhosis or in advanced stages<sup>[35-39]</sup>. Kim *et al.*<sup>[35]</sup> determined that OPN plasma level in HCC patients was significantly higher than in patients with chronic liver diseases or healthy controls (954 ng/mL *vs* 381 ng/mL; 954 ng/mL *vs* 155 ng/mL). Zhang *et al.*<sup>[36]</sup> also found that OPN plasma level of HCC patients was significantly higher than that of healthy controls (176.90 ng/mL *vs* 63.74 ng/mL). These data propose that elevated OPN plasma level can serve as a potential biomarker for HCC.

Meanwhile, several microarray studies have identified OPN-containing gene signatures of HCC patients<sup>[30-32]</sup>. Ye *et al.*<sup>[31]</sup> have identified *OPN* as a leading gene in the gene signature that was relevant to tumor metastasis and patient survival. Luo *et al.*<sup>[32]</sup> have found that overexpressed *OPN* gene belongs to a specific gene signature in HCC. In addition, many studies have established a significant correlation between OPN overexpression and clinicopathological features of HCC, including the severity of liver damage according to Child-Pugh class, high grade, late stage, LN/vascular/bile duct/capsular invasion, and intrahepatic or distant metastases<sup>[26-30,40-44]</sup>. Until now, OPN overexpression has been revealed as an independent prognostic factor for poor overall and disease-free survival in HCC patients<sup>[25-28,33,42-47]</sup>. In 2010, Weber

*et al.*<sup>[42]</sup> performed a meta-analysis and found that OPN level correlated with poor overall and disease-/relapse-free survival, and as a biomarker for stage, grade, and early tumor progression in HCC. Chen *et al.*<sup>[25]</sup> disclosed that OPN expression was a prognostic marker for HCC patients at TNM stage I. Furthermore, novel biomarker combinations are evaluated to predict patient outcome in HCC, since classical parameters cannot provide exact information. The biomarker combinations, OPN and  $\alpha$ -fetoprotein (AFP), or OPN and CD44s, are revealed to have better prognostic value than the classical diagnostic biomarkers<sup>[29,44]</sup>. Huang *et al.*<sup>[48]</sup> have suggested that the combination of OPN and caspase-3 can be an effective indicator for HCC patients after curative resection. However, because the published data are conflicting in many cases, further large-scale studies are necessary to confirm their clinical value<sup>[49]</sup>.

Tumor recurrence is a persistent issue after surgical resection. A number of studies have suggested OPN as a useful marker for predicting early recurrence in HCC patients<sup>[25-27,33,44-46,50]</sup>. OPN polymorphisms and the combination of OPN and CD44 are potential predictors of tumor recurrence in HCC<sup>[45,46]</sup>. OPN overexpression is associated with early recurrence of hepatitis C virus (HCV)-related HCC<sup>[50]</sup>. Chen *et al.*<sup>[25]</sup> found that OPN expression was correlated with early postoperative recurrence in patients at stage I. Sieghart *et al.*<sup>[33]</sup> have revealed that OPN is an independent predictor of tumor recurrence and survival in HCC patients beyond Milan criteria undergoing orthotopic liver transplantation. Thus, OPN may be able to help determine the patients who need adjuvant therapy to prevent early recurrence after surgical resection.

At present, many serum biomarkers are under evaluation for the detection of HCC, but none of them has sufficient sensitivity and specificity to be considered in the guidelines. OPN plasma level increases significantly with advanced Child-Pugh class, large tumor size, high grade, and late stage<sup>[35,38]</sup>. OPN plasma level is suggested as an adverse prognostic factor for both overall survival, disease-free survival and relapse-free survival in hepatitis

Table 1 Osteopontin as a potential therapeutic target for gastric and liver cancers

Cell lines	Mouse model	Method of study	Resultant effects	Possible mechanisms
Gastric cancer SGC7901	Nude mice	siRNA knockdown	Reduced angiogenesis <i>in vitro</i> and <i>in vivo</i>	Decreasing microvessel density
BGC-823	Nude mice	Transient/stable siRNA knockdown	Inhibited cell growth, anchorage-independent growth, migration and invasion <i>in vitro</i> , and suppressed tumor growth and prolonged survival <i>in vivo</i>	Inhibition of MMP-2 and uPA expression, NF- $\kappa$ B DNA binding activity, and Akt phosphorylation
SGC7901	Nude mice implanted with SGC-OPN-cells	Lentivirus-mediated stable depletion	Suppressed metastases and prolonged survival time <i>in vivo</i>	Reducing expression of VEGF
HCC MHCC97-L, MHCC97-H, HCC-LM3		siRNA knockdown	Decreased cell invasion and cell cloning number <i>in vitro</i>	
HuH1/4/7, MHCC97, SMMC7721, SK-Hep-1, Hep3B, CCL13, HCCLM3	Nude mice of lung metastasis	OPN-neutralizing antibody	Blocked invasion of SK-Hep-1 and Hep3B cells <i>in vitro</i> , inhibited pulmonary metastasis of HCC-LM3 cells <i>in vivo</i>	
HCC-LM6	Nude mice implanted with HCC-LM6	Antisense knockdown	Suppressed migration and invasion <i>in vitro</i> , decreased lung metastases <i>in vivo</i>	Inhibiting MMP-2 and uPA expression
HCC-LM3	Nude mice implanted with Lenti OPNi-transfected HCC-LM3 cells	Stable depletion using lentiviral vectors encoding miRNA against OPN	Inhibited both <i>in vitro</i> proliferation, invasion and <i>in vivo</i> tumor growth and lung metastasis	Inhibiting MAPK and NF- $\kappa$ B pathways, and MMP-2 and suppressing uPA expression
HCC-LM3 HepG2	Nude mice	shRNA gene silencing	Inhibited HCC cell growth, adhesion and invasion <i>in vitro</i> , and suppressed tumorigenicity and lung metastasis <i>in vivo</i> , enhanced sensitivity of HCC cells to chemotherapeutic drugs	Suppressing $\alpha$ , $\beta$ 1, $\beta$ 3 integrin expression, blocking NF- $\kappa$ B activation, inhibiting apoptosis

HCC: Hepatocellular carcinoma; OPN: Osteopontin; siRNA: Small interfering RNA; MAPK: Mitogen-activated protein kinase; NF: Nuclear factor; MMP: Matrix metalloproteinase; VEGF: Vascular endothelial growth factor; uPA: Urokinase-type plasminogen activator; shRNA: Short hairpin RNA; Akt: Protein kinase B; miRNA: microRNA.

B virus (HBV)- or HCV-related HCC patients<sup>[36,38,51]</sup>. In addition, OPN plasma level may be a potential diagnostic biomarker for HCC in the surveillance of patients with HBV or HCV infection. Sun *et al*<sup>[51]</sup> have suggested that preoperative plasma level of OPN and AFP can be used as a prognostic marker for early stage HCC. A recent study conducted by Shang *et al*<sup>[52]</sup> has also identified serum OPN as a novel marker for early HCC diagnosis because OPN was found clearly elevated 1 year before diagnosis in a pilot prospective study including 22 patients. In another two studies, a greater area under curve value of OPN than AFP was observed, suggesting superior diagnostic accuracy of OPN for HCC<sup>[58]</sup>. HCC patients whose pretreatment OPN serum level is low and declines following transarterial chemoembolization exhibit better tumor response and longer survival<sup>[37]</sup>. These data suggest that OPN plasma level can be used, either independently or coupled with AFP, for predicting clinical outcome in HCC patients.

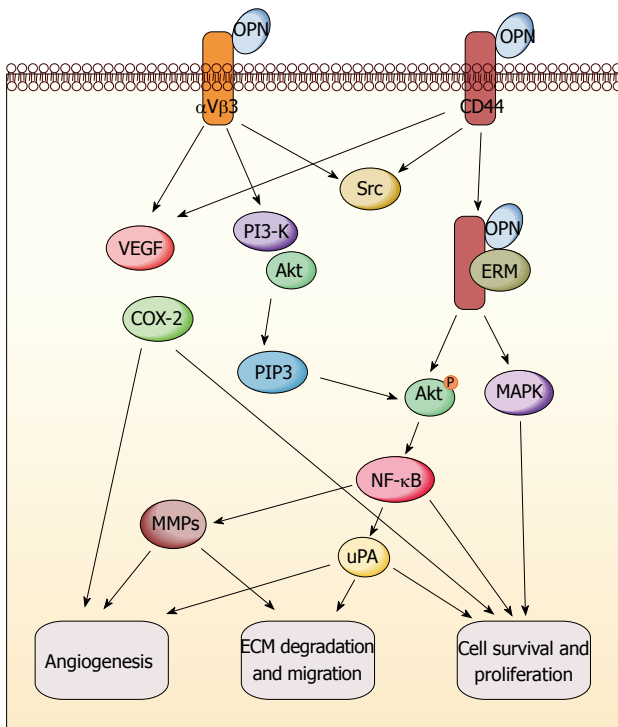
## OPN AS A POTENTIAL THERAPEUTIC TARGET FOR GASTRIC AND LIVER CANCERS

OPN as a therapeutic target has been explored in various tumors including cancers of breast, lung, head and neck, stomach, colon and liver. Promising results have been achieved in a series of studies<sup>[53-57]</sup>. The strategies often

utilize OPN antibody to block its binding to receptors so as to inhibit the downstream signal transduction related to tumor growth and invasion, and deliver the small interfering RNA (siRNA) targeting OPN to tumor cells to decrease directly the expression of OPN to abrogate the effects triggered by elevated OPN.

At present, OPN-knockdown-induced tumor suppression in gastric cancer has been shown through RNA interference (RNAi)<sup>[58-60]</sup>. *In vitro* and *in vivo* studies have demonstrated OPN-RNAi-induced inhibition of tumor growth, migration and invasion in gastric cancer<sup>[58,59]</sup>. Moreover, Wang *et al*<sup>[60]</sup> silenced OPN expression in gastric cancer cell line SGC7901 using lentiviral-OPN siRNA technology, and found reduced detectable tumors, fewer metastases, and longer survival time in mice implanted with OPN-SGC7901 cells. These data suggest that targeting OPN and its related signaling network is likely to provide an effective therapeutic approach for gastric cancer (Table 1).

In recent years, efforts have also been made to inhibit HCC progression and metastasis by interfering OPN<sup>[27,31,61-63]</sup>. OPN knockdown significantly suppresses migration and invasion of HCC cells *in vitro* and decreases lung metastases *in vivo*, which is associated with decreased angiogenesis in HCC cells<sup>[61,62]</sup>. Besides, OPN-specific antibody can effectively block HCC cell invasion *in vitro* and inhibit lung metastasis of HCC cells *in vivo*<sup>[31]</sup>. In addition, Zhao *et al*<sup>[63]</sup> have demonstrated that short hairpin RNA-mediated OPN depletion enhances sensitivity of HCC cells



**Figure 2 Molecular mechanisms of osteopontin in gastrointestinal cancers.** Osteopontin (OPN) signaling leads to gastrointestinal cancer growth and metastasis through activation of various pathways, including cell survival and proliferation, angiogenesis, and extracellular matrix (ECM) degradation. VEGF: Vascular endothelial growth factor; PI3-K: Phosphoinositide 3-kinase; COX-2: Cyclooxygenase-2; MAPK: Mitogen-activated protein kinase; NF: Nuclear factor; uPA: Urokinase-type plasminogen activator; MMP: Matrix metalloproteinase; ERM: Ezrin/radixin/moesin; Akt: Protein kinase B.

to chemotherapeutic drugs through blockade of nuclear factor (NF)- $\kappa$ B activation. Thus, targeting OPN and its related signaling network is likely to help develop novel therapeutic regimens for HCC (Table 1).

## MOLECULAR MECHANISMS OF OPN IN GASTRIC AND LIVER CANCERS

The multifunction of OPN has been revealed in promoting tumor formation and progression (Figure 2). It exerts these functions through direct binding to integrin and/or CD44. The subsequent activation of various pathways leads to increased malignant phenotype<sup>[64,65]</sup>. Various signaling transduction pathways triggered by OPN molecule have been reported in different cancer models such as breast cancer, melanoma, lung cancer, myeloma, prostate cancer and gastrointestinal cancers. The results indicated that OPN exerts the tumor-related functions through a complicated signaling network<sup>[65]</sup>. Here, we only summarize the reported signaling pathways of OPN relevant to gastric and liver cancers; some of which are commonly overlapped with other cancers, but some are specific in these two types of cancers. It has been suggested that phosphoinositide 3-kinase (PI3-K)/protein kinase B (Akt) pathway and hypoxia-inducible factor-1 are involved in the tumor-promoting function of OPN,

which induces pro-survival and anti-apoptosis signaling in gastric and liver cancers after the survival pathway is activated<sup>[63,66]</sup>. Mitogen-activated protein kinase pathway (MEK/ERK1/2) can also be triggered by OPN protein in liver cancer to promote tumor growth and metastasis, while the effect can be reversed through OPN knock-down<sup>[62]</sup>. The NF- $\kappa$ B pathway is crucial to keep cell survival through initiating the gene expression of antiapoptotic proteins, and is often induced by chemotherapeutic drugs and contributes to resistance to chemotherapy<sup>[59,62]</sup>. Relevant tumor-promoting functions of OPN are found to be highly associated with NF- $\kappa$ B pathway activation in gastric and liver cancers<sup>[59,62,63]</sup>. The MMP family is responsible for ECM degradation and remodeling, which plays an important role in tumor invasion and metastasis. OPN-induced metastasis of gastrointestinal cancers is also involved in several MMP members such as MMP-2, MMP-9, MMP-7 and other famous invasion-related proteins such as vascular endothelial growth factor (VEGF) and urokinase-type plasminogen activator (uPA)<sup>[54,59,62,67,68]</sup>. Recently, Lee *et al.*<sup>[66]</sup> illustrated that OPN can enhance the survival of gastric cancer through the interaction with CD44 variant isoforms. The underlying mechanism involves Src kinase signaling upon OPN binding to CD44, followed by “inside-out” integrin activation. In addition, there may be a positive correlation between OPN and cyclooxygenase-2 (COX-2). OPN, VEGF and COX-2 could synergistically induce angiogenesis and metastasis in gastric cancer<sup>[69]</sup>. On the other hand, the antitumor activity of COX-2 inhibitors in intestinal cancer is probably mediated through downregulation of OPN, which results from blockade of nuclear receptor subfamily 4, group A, member 2 (NR4A2) and Wnt/ $\beta$ -catenin signaling, two important components of the OPN regulatory network<sup>[70]</sup>.

Several mechanisms regulating *OPN* gene expression have been revealed, but many details remain to be elucidated. *OPN* is a transcriptional target of aberrant Wnt/ $\beta$ -catenin signaling<sup>[70-72]</sup>, and is also regulated by other molecules including specificity protein 1, v-ets erythroblastosis virus E26 oncogene homolog 1, runt-related transcription factor 2, v-myb myeloblastosis viral oncogene homolog, CDX2, deleted in liver cancer 1, late SV40 factor (LSF), epidermal growth factor (EGF), NR4A2 and NO<sup>[24,73-79]</sup>. Interestingly, the activation of several downstream targets of OPN, such as Akt, LSF, NO, EGF and thrombin, can enhance OPN expression in turn, suggesting a positive feedback regulation of *OPN* gene expression<sup>[68,73,78-82]</sup>. Moreover, the modulation of *OPN* mRNA stability also influences *OPN* expression in HCC<sup>[83,84]</sup>. In addition, miRNA-181a decreased *OPN* expression in HCC cell lines, suggesting that miRNA is involved in the regulation of *OPN* gene expression<sup>[85]</sup>. Furthermore, the expression of *OPN* is also affected by COX-2 and 30-kDa Tat-interacting protein<sup>[70,86,87]</sup>.

In short, OPN signaling could result in the activation of anti-apoptosis and pro-survival pathways *via* PI3-K-Akt and NF- $\kappa$ B signaling molecules, angiogenesis modulation *via* VEGF induction, ECM degradation *via* MMPs

and uPA secretion, leading to tumor growth and metastasis in gastric and liver cancers.

## CONCLUSION

OPN overexpression occurs frequently in patients with gastric cancer and liver cancer. Previous studies have revealed its clinicopathological correlation with tumor formation and progression in these two types of cancer, indicating its potential as an independent indicator for predicting outcome in such patients. Functional studies have shown the potential of OPN as a therapeutic target in gastric and liver cancers both *in vitro* and *in vivo*. OPN mediates multifaceted roles in the interaction between cancer cells and tumor microenvironment, in which many details need to be further explored. The various mechanisms of OPN signaling in gastric and liver cancers including evasion of apoptosis, modulation of angiogenesis, ECM degradation, activation of PI3-K-Akt and NF- $\kappa$ B pathways, might induce the development and progression of gastric and liver cancers. However, no clinical trial targeting OPN is in progress for tumor treatment, although the importance of OPN has been widely investigated and demonstrated in various cancers, and many patents including antibodies or peptides against OPN have been filed to treat different tumors. OPN is an important cytokine to mediate normal physiological functions. Blocking OPN possibly results in severe adverse effects due to interference with normal OPN roles. Therefore, further understanding of the implications and roles of OPN in various tumors including gastric and liver cancers could help develop better therapeutic strategies for such patients. On the other hand, OPN as a secreted plasma protein seems to have a greater potential to be utilized as a diagnostic or prognostic marker for in relevant cancers in combination with other biomarkers or alone.

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