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# Role of osteopontin in lung cancer evolution and heterogeneity

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ABSTRACT

Patients with lung cancer still have high mortality, recurrence rate after adjuvant treatment, and poor five-year survival rates, despite of advances in multidisciplinary anti-cancer therapies, e.g. chemotherapy, radiotherapy and targeted therapies, It depends upon the presence of intratumoral heterogeneity and complexity of lung cancer. There is growing evidence to suggest that osteopontin (OPN) may play a critical role in tumor progression and metastasis. The present review briefly describes the structure and molecular biology of OPN, highlights the role of OPN in the development and metastasis of lung cancer, and summarizes potential mechanisms of OPN heterogeneity in tumor to underline some of these inconsistencies. The article will emphasize the importance to understand the role of OPN in cancer evolution and heterogeneity and explore the potential of OPN as a therapeutic target.

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## 1. Introduction

Osteopontin (OPN) is a secretory extracellular matrix glycosylated phosphoprotein which was first identified in bone tissue as a major sialoprotein to modulate bone formation and remodeling [1]. It is a member of small integrin-binding ligand N-linked glycoproteins, a family of five integrin binding glycophosphoproteins, e.g. bone sialoprotein, dentin matrix protein 1, dentin sialophosphoprotein, and matrix extracellular phosphoglycoprotein [2]. OPN was found to contribute various metastasis-associated mechanisms, including proliferation, survival, adhesion, migration, invasion and angiogenesis [3,4].

The importance of OPN in tumor dissemination is highlighted by the fact that transfection of OPN could increase malignant phenotype [5] and OPN knock-out with antisense oligonucleotides decrease malignant potential [6]. OPN is expressed in human multitissues and over-expressed in multiple cancer types. For example, OPN was up-regulated in non-small cell lung cancer (NSCLC) [7] and even more in cells with strong potential and capacity of metastasis and invasion [7,8], which could down-regulated by the deletion of OPN [9]. The up-regulation of OPN has been proposed to be associated with stages, severities, lymph node metastasis, poor prognosis, and high recurrence [10–12].

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OPN plays an important role in metastasis of NSCLC, although OPN functions still need to be further investigated and confirmed. There are more needs to understand the existence of OPN heterogeneity in lung cancer and involved molecular pathways and mechanism of OPN-induced tumor heterogeneity. The present article overview whether the heterogeneity of OPN and correspondent receptors exists in cancers and contributes to mechanisms by which cancer cells have varied functions and responses to therapies. The present review briefly describes the structure and molecular biology of OPN, highlights the role of OPN in the development and metastasis of lung cancer, and figures out the heterogeneity of OPN in lung cancer.

## 2. OPN structure and molecular biology

### 2.1. Structure of OPN

The OPN gene (SPP1; Secreted Phosphoprotein 1) is allocated to human chromosome 4 (4q13) with 7 exons and to mouse chromosome 5 at the ric$^{r}$ locus [13]. OPN is a 32 kDa protein with an extensive modification during post-translation and with electrophoretic mobility between 44 and 75 kDa, including phosphorylation and N-linked glycosylation [14,15]. OPN is referred as Intrinsically Disordered Proteins as a class of biologically active proteins lacking defined secondary and tertiary structure [16]. The conformational flexibility of OPN deviates from random coil-like behavior, although OPN does not fold into a single defined structure. OPN protein is acidic, hydrophilic, and highly negatively charged with features of a secreted protein lacking a membrane anchoring domain [17]. OPN comprises distinct local secondary structure elements with reduced conformational flexibility and displays distinct tertiary contacts and binds with integrin and heparin [18]. Human OPN has a typical RGD domain and a second integrin-binding site SVVYGLR (i.e. serine-valine- valine- tyrosine-glycine-leucine-arginine) [19,20] that ligate cell-surface αvβ3, αvβ1, αvβ5, α5β1 or α9β1 integrins (Fig. 1). Additional calcium binding site, two consensus heparin binding domains, and run of 9–10 aspartate residues of OPN represents an hydroxyapatite binding sequence [20]. The heterogeneity of OPN phosphorylation, glycosylation and sulphation can contribute to different forms of OPN functions and tissue specificities [21]. OPN contains a thrombin cleavage site within six amino acids of the RGD sequence [22].

### 2.2. Regulation of OPN

OPN is structurally and functionally modulated by proteolytic processing. A number of signaling pathways can activate OPN, including oncogenic, tumor promoting pathways, e.g Wnt/β-catenin, Hedgehog, NF-κβ, G-protein coupled pathways, receptor tyrosine, or/and estrogen signaling pathways (Fig. 1). Of those, Ras-response factor forms a complex with the Ras-activated enhancer and is stimulated by Ras signaling in fibroblasts and epithelial cells [23]. The T cell factor-4 (Tcf-4) binding site in the SPP1 promoter can retard OPN transcription after the binding with Tcf-4 protein. Human SPP1 promoter region from −94 to −24 can bind transcription factors, e.g Sp1, Myc, or Oct-1, which may act synergistically to stimulate OPN transcription in malignant astrocytic cells [23]. Up-regulation of aryl hydrocarbon receptor (AhR), a transcription factor activated by xenobiotics, up- regulates OPN expression in lung cancer [24]. Ligand-independent and ligand-activated AhR can activate the −268 to +435 region of SPP1 promoter [24]. In addition, OPN promoter's responsiveness to β-catenin and Lef-1 was enhanced by Ets transcription factors such as Ets-1, Ets-2, ERM, or PEA3 [25]. Expression of OPN could be trans-activated by the Tax protein of HTLV-1 [26] or estrogen related receptor [27]. Wnt signaling, NF-κβ and the Hedgehog pathways also play critical roles in regulation of OPN transcription [28–30].

There are many repressors to mediate intricate spatiotemporal regulation of OPN transcription (Fig. 1). BRCA1 could selectively bind estrogen receptor alpha, AP-1, and PEA3 to inhibit OPN promoter transactivation, while mutant BRCA1 upregulates OPN protein [31]. Breast cancer metastasis suppressor 1 protein could reduce OPN mRNA and protein expression, at least in part, responsible for Breast cancer metastasis suppressor 1-mediated metastatic suppression by sensitizing cancer cells to stress induced apoptosis [32]. The interferon-induced transmembrane protein 3 gene was found to reduce OPN mRNA expression and negatively impact cell adhesion, cell invasion, or metastasis [33]. RUNX3 is also a transcriptional repressor of OPN to promote migration of gastric cancer cells [34]. The repression of OPN is also caused by epigenetic regulators such as miRNA-181a in hepatocellular carcinoma [35] and by hsa-mir-299-5p in breast cancer stem-like cells [36].

### 2.3. Molecular biology of OPN

OPN is isolated and characterized as a major phosphoprotein and associated with bone metabolism and malignant disease. OPN acts as an osteoclast autocrine motility factor and binds to the integrin αvβ3 and CD44 during stimulation of osteoclast migration [37]. OPN also stimulates bone resorption of osteoclasts, and induces osteoporosis [38,39]. OPN can inhibit tissue or dystrophic calcification and formation of kidney stones [40]. OPN was originally identified and cloned as an early T cell activation-1, a cytokine expressed by activated CD4+ T cells [41]. OPN caused the migration of macrophages, suppressed the production of reactive oxygen species, to further stimulate B cells to produce immunoglubulins [42]. OPN is recognized as a pleotrophic cytokine [43] and functions from pro-inflammatory effects (e.g. inducing macrophage chemotaxis and type-1 cytokine expression) to anti-inflammatory effects (e.g. inhibiting iNOS expression) [42]. OPN is studied as an important prognostic marker in a variety of cancers and acts as a key regulator in tumor proliferation, survival, migration, invasion and angiogenesis [3,4]. OPN can also modulate cell-mediated immunity and granuloma formation, tissue repair, and fibrosis, as well as atheromatous plaque formation [44–46].

## 3. Roles of OPN in lung cancer development and metastasis

### 3.1. Expression of OPN in lung cancer

OPN over-expresses in a variety of cancers and is associated with disease progression and outcome [47,48]. For example, OPN was up-regulated in lung carcinoma cells and associated infiltrating inflammatory cells [49] and suggested as a prognostic biomarker in NSCLC. OPN immunoreactivity is higher in NSCLC (37%), especially in squamous cell cancer (SCC) (68%), as compared with small cell lung cancer (SCLC) (11%) and normal lung [49]. OPN was principally expressed in NSCLC cells (H322 cells and HL460 cells), rather than in SCLC derived cells (H69 cells).

Circulating levels of OPN were higher in patients with lung neoplasm and were suggested as a biomarker to diagnose lung neoplasm in certain population groups [50]. Our group investigated genetic variations, specific signal pathways, biological processes of chromosome 4 genes between subtypes and stages of lung cancer, and prediction of selected targeting genes for patient survival rate. We integrated and analyzed about 537 patients with lung adenocarcinoma (ADC), 140 with SCC, 9 with lung large-cell carcinoma (LCC), 56 with SCLC, and 590 without cancer from 16 databases, and found that OPN significantly up-regulated more than 2 fold in

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