Review Article

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Dentistry Section

OPN –Revisited

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ABSTRACT

Osteopontin (OPN), a matrix extracellular glyco-phosphoprotein is found in various tissues such as epithelium lined tissues, kidney, bone and teeth .It is also detected in all body fluids including blood and breast milk. OPN plays role in a number of physiological and pathologic events such as cell adhesion, migration and cell survival, angiogenesis, apoptosis, inflammation and wound healing. This review summarizes the current data of the biological activities of OPN in the development of tumour, its progression and metastasis.

Keywords: Angiogenesis, Cell adhesion, Metastasis, Osteopontin

INTRODUCTION

Osteo" means bone; "Pontin" is a Latin word derived from "Pons" meaning bridge [1]. The term "Osteopontin" reflects the potential to bridge hydroxyapatite with cells [2]. It is a SIBLING glycoprotein [3] that was first identified in 1986 in an Osteoblast. OPN was first described by Senger et al., as a secreted 60KDa transformation specific phosphoprotein [4].

OPN was discovered in the extracellular matrix of bone, along with bone sialoprotein. It was initially referred to as Bone sialoprotein I and Bone sialoprotein II respectively. These proteins are heavily glycosylated and phosphorylated with high levels of acidic amino acids. Asparatate is predominant in Osteopontin. OPN has a specific amino acid sequence (Arg-Gly-Asp) and is also termed RGD-containing protein. The pleiotropic effects of OPN mediated by the different receptors provide the basis for its emergence [5]. An alternate name-"Secreted phosphoprotein" (SPP 1) reflects a broader function of this protein. Although many nomenclatures have been suggested for this protein, the term OPN has been retained to refer for the same. The activated lymphocytes & macrophages produces putative lymphokine which contains the same gene product as was identified and referred to as Eta-1(Early T lymphocyte activation 1) [5,6].

Genomic Location & structure

The molecular weight of OPN is 44 KD to 66 KD depending on species and cell types [5]. OPN is expressed by a single-copy gene as a 34-kDa nascent protein composed of 300 amino acid residues. The human gene contains 7 exons and maps to the long arm of chromosome 4 (4q21-23) [4]. In mouse, the gene is situated at chromosome 5 locus of the Rickettsia resistance gene and the pig gene is on chromosome 8. In the mammalian cells, a similar number of amino acids are present in the protein, the size of which ranges from 44kD to 75kD after the post-translational modifications [4].

The OPN protein is a high negatively charged secreted protein which is hydrophilic and acidic in nature. The polyaspartic acid motif of this protein helps in binding the protein to hydroxyapatite, calcium ions and RGD sequence which in these mediates cell attachment [7]. OPN is a 16 amino acid hydrophilic leader sequence lacking a membrane anchoring domain. The eight alpha helices and six segments of beta sheets may form the secondary structure of OPN. OPN contains RGD cell-binding domain that is presented in many extracellular matrix proteins and is critical for Integrin binding. The RGD site is flanked by a 50 amino acid sequence that is similar to that surrounding the RGD motif in fibronectin.

POST-TRANSLATIONAL MODIFICATIONS

Post-translational modifications can have significant effects on the structure of the OPN molecule. Different functional forms of OPN done to variations in glycosylation, sulphation and phosphorylation may be found in the same or different tissues [8].

Increased anionic surface characteristics can be obtained by phosphorylation and sulphation while this flexibility can be limited by glycosylation. Phosphorylation reaction can take place on tyrosine/serine & threonine residues. These modifications can also affect the structure & properties of OPN including signaling activities [9].

Phosphorylation can be prevented by glycosylation of OPN which in turn prevents the invasion of cancer cells. Sulphation of OPN occurs predominantly in high phosphorylated form of OPN. This has been suggested as a potential marker for a differentiated Osteoblast. A non-sialylated to a sialylated cellular transformation in oncogene transfected cell suggests the post-translational modifications of OPN [4].

OPN IN NORMAL TISSUES

OPN is one of the most abundant non-collagenous, non-specific proteins in bone.OPN is expressed in a variety of tissues such as bone, bone marrow derived gland cells, cartilage, dentine, cementum, kidney, brain, vascular tissues, specialized epithelia found in mammary, salivary, sweat glands, in bile and pancreatic ducts, in distal renal tubules, gut, as well as in activated macrophages and lymphocytes. OPN is also found in biological fluids such as milk, urine, blood and seminal fluid [7].

The OPN can detect on the surfaces of mature bone trabeculae and the cemental lines [3]. It accumulates at the interfacial structures and cell-matrix in bone. Therefore OPN has several functions including control of mineralization, coupling of bone formation, the attachment of osteogenic cells to the bone matrix and resorption. It is also expressed by fibroblast in embryonic stroma and the sites of wound healing [8].

Regulation

The expression of OPN is up-regulated by various factors

(i) Hormones includes steroids, retinoic acid, glucocorticosteroids and 1,25-dihydroxy vitamin D3.

(ii) Inflammatory cytokines.

(iii) Growth & differentiation factors such as epidermal growth factor (EGF), platelet-derived growth factor, transforming growth factor-Beta (TGF-β).

These factors influence the rate of gene transcription, mRNA processing, stability and translation as well as post-translational modifications maturation [9].

The down-regulation of OPN by bisphosphonates occurs in bone and kidney. OPN expression is suppressed in vascular smooth muscle cells by cGMP-dependent protein kinase which is a mediator of nitric oxide and cGMP signaling.

Functions

OPN is a multifunctional molecule that is involved in both physiological and pathological processes. The important physiological role played by OPN is bone remodeling, calcification, immune response, inflammation, regulation of cell adhesion migration and cell survival. OPN has been recognized as an important luminal regulator due to its expression by epithelial cells covering luminal cavities capable of active secretion and absorption of nutrients [6].

Cell attachment and signaling through integrins

Most of cells adhere to OPN through integrins. Both αv (β1,β3,β5) and (α4,α8,α9) β1 on several cell types bind to OPN. The amino- and carboxy-terminal parts of OPN non-GRGDS (Gly-Arg-Gly-Asp-Ser) region also mediate cell attachment. The αvβ3 Integrin which can be regulated with OPN is believed to be primarily responsible for the adhesion and migratory properties. It can also generate intracellular signals through autocrine and paracrine mechanisms of αvβ3 though inner or outer signaling may be needed to stimulate adhesion and migration [1].

Cell attachment and signaling through CD44

OPN is also an extracellular ligand for CD44 & its various isoforms which is the main cell surface receptor for hyaluronate. However, CD44 is expressed in osteoblast, osteocytes, osteoclasts, epithelial cells, endothelial cells fibroblasts and smooth muscle cells [10]. The CD44 family of receptors which are implicated in several cellular responses along with β1 containing integrins to bind multiple sites in OPN and bring about motility and chemotaxis of the immune cells. This has been implicated in not only repair and regenerative processes but also tumour survival, growth and progression [11].

The Role of OPN in Angiogenesis

The formation of new blood vessels is referred to as Angiogenesis. OPN binds to the αvβ3 integrin that signals the survival and differentiation of vascular cells during angiogenesis. The expression of OPN and αvβ3 Integrin has been found to be increased during periods of repair and regeneration. OPN via NF- KB pathway activation protects the endothelial cells from apoptosis [12].

OPN and Pathological Conditions

The OPN expression is found in various pathological conditions such as pathological calcifications of soft tissues, cardiovascular diseases and kidney diseases. It is also observed that formation and mineralization in normal and pathological situations due to the presence of polyaspartic acid moieties and the phosphate groups [3].

In non bone tissues, OPN expression occurs only in response to stimulus such as inflammation. During inflammation, OPN is secreted by T-lymphocytes and activated macrophages. OPN is also secreted by the proliferating fibroblasts and myofibroblasts during granulation tissue formation [1]. Secretion of OPN under these conditions has been correlated with increased tissue calcification. In the absence of OPN expression, macrophage migration and adhesion are impaired while the ability of OPN to promote fibrosis is consistent with improved wound healing. OPN promotes survival of fibroblasts, as well as endothelial cells involved in neo-vascularization [13].

In fibroblastic cells, the lack of OPN expression leads to caspase-independent necrosis, promoted by oxidants. In contrast to programmed cell death where dying cells undergo phagocytosis and clear the way for new tissues and cells, necrotic cell death is strongly associated with an exacerbation of inflammation and an increase in tissue destruction. Cell necrosis is a rapid form of cell death in which damage and rapid permeabilization of cell membranes lead to the release of intracellular contents. The released cellular components act as irritants, recruiting more phagocytes (PMN, macrophages) and aggravate inflammation resulting in tissue destruction. The formation of granulation tissue and the intensity of inflammatory reactions are dramatically reduced in the absence of OPN expression [14].

The adaptive immune system is based on a specific recognition between the antigen-presenting cells and naïve T-cells, resulting in the differentiation of Th1, T-helper, and cytotoxic (NKT) T-cells, which control the immune reaction. Studies have correlated OPN expression with epithelial barrier changes with macrophage, neutrophil and lymphocyte activities and with the function of reparative fibroblasts [13]. Therefore, there is presence of OPN in diseased and injured tissue.

OPN and Cancer

OPN contains a well-recognized adhesion domain Arginine-Glycine-Aspartic acid, which can interact with specific Integrin receptors, as well as other adhesion regions. OPN & its receptor complexes along with VEGFR2 activate PI3k/PKB pathway which leads to the activation of eNOS/NO signaling. Simultaneously, VEGFR2 can also signal through PLCγ leading to increased eNOS phosphorylation and NO production which in turn increases the endothelial cell survival, proliferation, migration, and permeability. These complexes also mediate motility & invasion of tumour cells through the activation of the MEK/Erk pathway. Similarly, these complexes inhibit tumour cell proliferation through the activation of the TGFβ/smad pathway and induce apoptosis of tumour cells. Secreted Protein Acidic and Rich in Cysteine (SPARC) binds integrin, inducing ILK/FAK/PKB activation to increase cell migration. Cyr61 can promote tumour cell proliferation and survival through the activation of integrin mediated signaling pathway either by direct binding with integrin or integrin-syndecan [2]. The interaction of OPN in the intracellular events of the FAK/PI3K/PKB signaling pathway may be either nuclear translocation of β-catenin or phosphorylation of GSK3β /NF-κB survival pathway for cell proliferation. These aspects of OPN have been clinically and functionally associated with various cancers. Clinically, there are numerous studies showing OPN expression in both tumour cells and cells found within the tumour microenvironment [14]. OPN expression in tumour cells has been shown in a variety of cancers including carcinomas of breast, prostrate, colon, ovary, stomach, cervix, lung, mesotheliomas as shown in [Table/Fig-1].

Author	Tumour	Study
Brown et al., [15]	Colon,stomach,duodenum, pancreas,duodenum, breast,lung,bladder, prostrate,ovary	In northern blot analysis-OPN mRNA & OPN protein by IHC detected but not detectable by ISH
Teruyoshi et al., [16]	Gastric carcinoma	In northern blot, ISH and IHC analysis- the OPN mRNA was over expressed of OPN was correlated with the progression of human gastric carcinoma.
Devoll et al., [17]	Premalignant and malignant lesions arising from oral epithelium.	Positive expression of OPN mRNA found using Northern blotting
Agarwal et al., [18]	Colon cancer	In oligonucleotide expression array, northern blot analysis and IHC. IHC technique-a highly significant correlation was found in colon cancer and adenomas (advanced staging)

Rudland et al., [19]	Breast cancer (stage I &II)	Western blotting technique and IHC results suggest that the OPN is tightly correlated with patient demise.
Coppola et al., [20]	Breast, Ovary, Endometrium, esophagus, stomach, pancreas, bileduct, liver, colon, kidney, bladder, prostate, Head& neck, salivary gland, lung, skin and brain	Significant OPN staining in a large percentage of the gastric, colon, pancreatic, renal, lung, endometric, esophageal, head and neck tumours The strong correlation between pathological stage and OPN across multiple tumour types suggested its role in tumour progression
Celetti et al., [21]	Laryngeal Squamous cell carcinomas	In IHC, immunoblotting and RT-PCR - the OPN expression was closely correlated with advanced stage, high grade metastatic disease and poor survival
Donati et al., [22]	Non-small cell lung cancer (stage I)	In IHC- high OPN expression associate poor survival rate with non –small cell lung cancer
Kita et al., [23]	ESCC	In IHC-the OPN expression is useful for predicting the malignant properties of ESCC.
Matsuzaki et al., [24]	Squamous cell carcinoma(SCC) of the tongue	OPN immunohistochemical staining showed a remarkable increase at the invasion front compared with the non-invaded regions
Tigrani et al., [25]	Epithelioid mesotheliomas & reactive mesotheilal proliferation	The immunohistochemical expression of OPN usefulness in distinguishing reactive mesothelial proliferation from malignancy
Chien et al., [26]	Tongue cancers (T1&T2)	The positive expression of OPN significantly correlated with relatively advanced, nodal status, tumour necrosis and tumour thickness
WU et al., [27]	ESCC	OPN was associated with the development of ESCC, but no significant associations between these protein expressions and patient's cancer stage or survival.
Zhang et al., [28]	Epithelial ovarian tumours	The positive immune reactivity of OPN &B7-H4 was higher in poorly differentiated ovarian cancer than in medium and highly differentiated ovarian cancer
Ogbureke et al., [29]	Oral Premalignant Lesions	Bone sialoprotein and Dentin Sialophosphoproteins expression pattern correlated with decreased transformation to OSCC.
Han WH et al., [30]	Human nasopharyngeal carcinoma	In IHC &western blotting methods- OPN expression significantly related to tumour size, regional lymph node metastasis

[Table/Fig-1]: OPN studies in various tumours

OPN and Tumour Microenvironment

The tumour microenvironment is an essential element of the success of any cancer. OPN produced by other cells in the tumour micro environment, such as macrophages and stromal cells [31], has been seen in a number of different cancer types as well. For example, In lymph node negative breast cancer patients, OPN mRNA and protein were detected in both tumour cells and tumour infiltrating inflammatory cells [32]. Masloub et al., concluded that the high CD10 and Osteopontin expression indicate the neoplastic potential, locally invasive behaviour and their high risk of recurrence.

OPN and Metastasis

Metastasis is a process that is inherently associated with malignant tumours and has a complex pathway where the tumour cells migrate to distant sites of the body. This is brought about by cell-cell interactions and tumour seeding through neovascularization [33]. This process requires the presence of Adhesion molecules including OPN Integrin-mediated cancer cell migration, angiogenesis, inhibition of apoptosis and ECM degradation via MMPs in Cancer metastasis [29,30,34-36]. There have been numerous studies determining how OPN levels in tumour tissue and patient's plasma/serum correlate with survival in a variety of cancers [Table/Fig-2]. The OPN levels, whether in tumour tissue or patient plasma, may provide useful prognostic information. Thus OPN can be used as a good biomarker to monitor disease progression.

Author	Tumour	Study
Fedarko et al.,[37]	Prostate, colon, breast, lung carcinomas	In competitive ELISA assay, provided a high degree of sensitivity and specificity informative markers the detection of colon, breast, prostate & lung cancer
Kim et al., [38]	Epithelial ovarian cancer	Plasma OPN were significantly higher in epithelial ovarian cancer (486.5ng/ml), benign lesion (254.4ng/ml)& compared with healthy controls (147.1ng/ml)- RT-PCR & ELISA
Katakura et al.,[39]	Oral cancer	The elevated levels of interleukins-IL-1β, IL6, IL8 and OPN in the saliva of the oral cancer patient by ELISA method
Thu Le Q et al.,[40]	Head & neck Squamous cell carcinoma	Significantly higher plasma OPN levels correlates relapse, survival rate and tumour recurrence
Koopmans et al.,[41]	Pancreatic adenocarcinoma	Serum OPN levels were elevated in pancreatic adenocarcinoma as a diagnostic marker
Bramwell et al.,[42]	Metastatic breast cancer	The increased level of OPN were strongly associated with poor survival and used in making treatment decisions
Petrik et al.,[43]	Head and Neck Squamous cell carcinoma	Plasma OPN level was elevated in uncontrolled tumour (642ng/ml) correlates tumour control rate, event –free survival and post relapse survival
Cho et al., [44]	Cervical cancer	plasma OPN levels are potentially useful as diagnostic and prognostic biomarker for cervical cancer
Zhou et al.,[45]	Oral Lichen Planus-premalignant lesion	In ELISA, The serum concentration of OPN and TNF- α were significantly higher in OLP patient than the normal control

[Table/Fig-2]: OPN studies in various body fluids -plasma, serum & salivary secretion

CONCLUSION

Cancer remains a significant global public health concern. This review emphasizes the biological role of OPN in many aspects of tumour biology. For research to progress, OPN will shed light on a tumour and stroma-derived therapeutic target to various Cancer.

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