POSSIBLE RELATION BETWEEN OSTEOPONTIN AND THYROID GLAND DISORDERS

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Abstract

Thyroid diseases are considered of the most common and important endocrinological disorders that are associated with multiple deleterious effects. Osteopontin (OPN), a molecule first identified in osteoblasts, is a multifunctional protein involved in inflammation, cell adhesion & remodeling. It has been suggested that OPN plays a role in many diseases. Thyroid dysfunctions are the most common endocrine problems encountered in clinical and endocrinology laboratory. Hyperthyroidism and hypothyroidism together are responsible for considerable morbidity in over 110 countries of the world among them most are developing countries. Osteopontin (OPN) is a molecule first identified in 1986 in osteoblasts and is known to be involved in the formation and calcification of bone. OPN is expressed in higher levels in papillary thyroid carcinoma and its expression levels were significantly associated with higher tumor size and presence of vascular invasion. OPN can be used as a biomarker in thyroid cancer, besides being a putative target for papillary thyroid cancer therapeutic approaches.

Keywords: Osteopontin, Thyroid gland Disorders

Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

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DOI: 10.53555/ecb/2023.12.Si12.238

Introduction:

Osteopontin (OPN) is a molecule first identified in 1986 in osteoblasts and is known to be involved in the formation and calcification of bone. OPN has important roles in physiological as well as pathological processes **(1).**

The prefix of the word "osteo" indicates that the protein is expressed in bone and the suffix "-pontin" is derived from "pons," the Latin word for bridge, and signifies osteopontin's role as a linking protein **(2).**

OPN is a highly negatively charged secreted protein, phosphorylated glycophosphoprotein which is rich in aspartic acid and has acidic characteristics consisting of 300 amino acids and including O-linked and N-linked oligosaccharides **(3).**

It is accepted that OPN has an arginine-glycine-aspartic acid binding zone, 2 heparin binding zones, one thrombin binding zone and one calcium binding zone. Moreover, matrix metalloprotease 3 and 7 (MMP-3,7) are also linked to OPN. Osteopontin has two terminal zones including N-terminal and C-terminal. C-terminal binds two heparin molecules as well as CD44 variants whereas N-terminal includes integrin receptor binding zones **(4).**

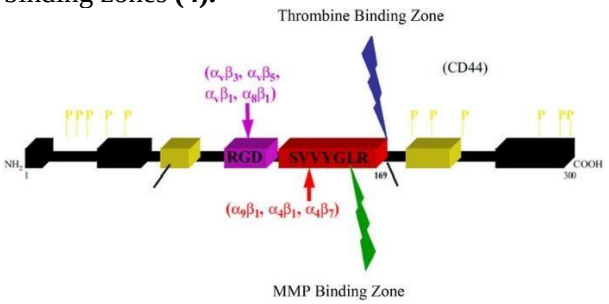

Figure-1:- Structural form of osteopontin.

Biogenesis of OPN:-

OPN is encoded by the secreted phosphoprotein 1 (SPP1) gene, a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family along with four other genes, dentin matrix protein 1 (DMP1), dentin sialophosphoprotein (DSPP), integrin-binding sialoprotein (IBSP), and matrix extracellular phosphoglycoprotein (MEPE). SIBLINGs are codirectional tandem genes located within the 37.5 kb region of human chromosome 4q21–25, and the SPP1 gene spans 7.8 kb in length with seven exons. The sixth exon is an exposed arginine-glycine-aspartate (RGD) domain that typically encodes more than 80% of the OPN protein **(5).**

The selective splicing of the human SPP1 pre-mRNA produces, five OPN isoforms (OPN-a, OPN-b, OPN-c, OPN-4, and OPN-5). These different isomers show specific expression in different cellular environments and have different biological functions. Upregulation of *Spp1* gene expression is frequently associated with inflammation elicited by events, including but not limited to infections, allergic responses, autoimmunity and tissue damage. OPN plays an important role in immune responses of different immune cell types, including both lymphocytes and myeloid cells **(6).**

Tissue distribution:-

Osteopontin (OPN) is a multifunctional noncollagenous matrix phosphoprotein that is expressed both intracellularly and extracellularly in various tissues, including epithelial cells, endothelial cells, fibroblasts, pericytes, hepatocytes, lens cells, tubular cells, immune cells (such as T cells, B cells, macrophages, natural killer, natural killer T, and Kupffer cells), neural cells (such as neurons, glial cells, and Schwann cells), osteoblasts, osteoclasts, and vascular smooth muscle cells. Synthesis of osteopontin is stimulated by calcitriol (1,25-dihydroxy-vitamin D_3) **(7).**

The OPNs produced by those cells are involved in various physiological and pathological processes, including wound healing, biomineralization, bone remodeling, vascularization, diabetes, obesity, inflammation, fibrosis, urolithiasis, autoimmune diseases, tumorigenesis, and cancer invasion and metastasis. The pleiotropic effect of OPN on these many cellular processes is mainly due to its functional activities, including cell adhesion, migration, proliferation, survival, differentiation, inflammatory cell activation, and immune modulation **(8).**

Regulation:-

Regulation of the osteopontin gene expression is incompletely understood. Different cell types may differ in their regulatory mechanisms of the OPN gene. OPN expression in bone predominantly occurs by osteoblasts and osteocyctes (bone-forming cells) as well as osteoclasts (bone-resorbing cells). Runx2 (aka Cbfa1) and osterix (Osx) transcription factors are required for the expression of OPN Runx2 and Osx bind promoters of osteoblast-specific genes such as *Col1α1*, *Bsp*, and *Opn* and upregulate transcription **(9).**

Hypocalcemia and hypophosphatemia (instances that stimulate kidney proximal tubule cells to produce calcitriol (1α,25-dihydroxyvitamin D3)) lead to increases in OPN transcription, translation and secretion. This is due to the presence of a high-specificity vitamin D response element (VDRE). Also, Pro-inflammatory cytokines stimulate osteopontin gene transcription and expression. Other mediators that can induce OPN upregulation

include angiotensin II, transforming growth factor β(TGFβ), tumor necrosis factor α (TNFα), interleukin-1β (IL-1β), nitric oxide (NO), hyperglycemia and hypoxia **(10).**

Due to differences in post-translational modification (PTM) (phosphorylation, glycosylation, sulfation and proteolysis) from different cellular sources, OPN has a molecular weight ranging from 41 to 75 kDa, which may have a cell type-specific structure and function **(11).**

Initially identified in osteosarcoma cells, OPN was reported to play a critical role in bone synthesis and resorption by mediating osteoblasts adhesion. Later, OPN was found as early T lymphocyte activation-1 (Eta-1) because activated T cells express copious OPN **(6).**

OPN was not only found to be involved in the formation and calcification of bone, but also in processes like inflammation, cell adhesion and migration and prevention of apoptosis because of its expression by various other tissues of the body. It is suggested that osteopontin plays a role in many diseases such as chronic inflammation, including Crohn's disease, several types of cancer, autoimmune diseases, Grave's disease, obesity, atherosclerosis and cardiac fibrosis **(2).**

Functions of Osteopontin:-

OPN functions as a free cytokine in body fluids or as an immobilized extracellular matrix molecule in mineralized tissue. Its pleiotropic effects are partly due to its capacity to interact with multiple ligands including several cell surface receptors, intracellular signaling molecules, calcium, and heparin. The binding sites to cell surface receptors include a RGD (arginine–glycine–aspartate) motif interacting with integrins αvβ1, αvβ3, αvβ5, αvβ6, α8β1, and α5β1 **(12).**

Immune system

OPN binds to several integrin receptors including α4β1, α9β1, and α9β4 expressed by leukocytes. These receptors have been well-established to function in cell adhesion, migration, and survival in these cells.

Osteopontin (OPN) is expressed in a range of immune cells, including macrophages, neutrophils, dendritic cells, microglia and T and B cells, with varying kinetics. OPN is reported to act as an immune modulator in a variety of manners. Firstly, it has chemotactic properties, which promote cell recruitment to inflammatory sites. It also functions as an adhesion protein, involved in cell attachment and wound healing. In addition, OPN mediates cell activation and cytokine production, as well as promoting cell survival by regulating apoptosis. The following examples are found **(13).**

Crosstalk between innate and adaptive immunity:-

The role of OPN in the crosstalk between innate and adaptive immunity is clearly highlighted in the development of pro-inflammatory T helper (Th) type-1and Th17 cells. By acting on macrophages, OPN upregulates interleukin- (IL-12) production and enhances Th1 development. By acting on Th cells, OPN induces produc- tion of IL-17 by triggering αvβ3 integrin and inhibits secretion of IL-10 by triggering CD44. By interacting with CD44 in Th cells, OPN induces hypomethylation of interferon- (IFN-) γ and IL-17a genes enhancing differentiation of Th1 and Th17 cells. In contrast, CD44 deficiency promotes hypermethyla- tion of IFN-γ and IL-17a and hypomethylation of IL-4 gene, leading to Th2 cell differentiation **(14)**

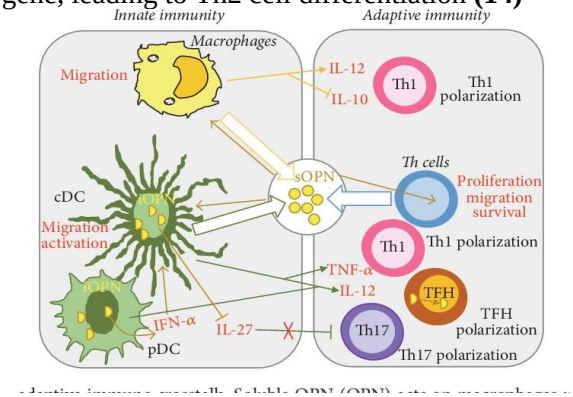

Figure 2: OPN mediates innate-adaptive immune crosstalk (14)

Also, OPN binds to several integrin receptors including α4β1, α9β1, and α9β4 expressed by leukocytes. These receptors have been well-established to function in cell adhesion, migration, and survival in these cells.

Cell activation:-

Osteopontin (OPN) is expressed in a range of immune cells, including macrophages, neutrophils, dendritic cells, microglia and T and B cells, with varying kinetics. OPN is reported to act as an immune modulator in a variety of manners. Firstly, it has chemotactic properties, which promote cell recruitment to inflammatory sites. It also functions as an adhesion protein, involved in cell attachment and wound healing. In addition, OPN mediates cell activation and cytokine production, as well as promoting cell survival by regulating apoptosis. The following examples are found **(13).**

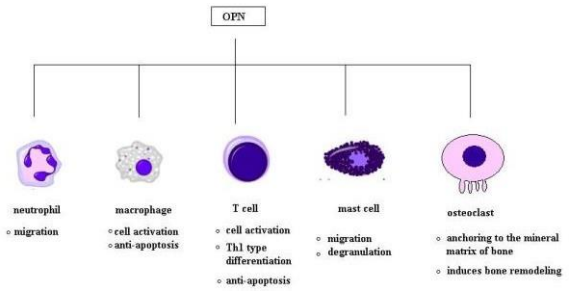

Figure-3:- Known immunologic functions of OPN **(13).**

Biomineralization:-

OPN also has a large number of consensus sequence sites for post-translational phosphorylation of Ser residues to form phosphoserine, providing additional negative charge. Contiguous stretches of high negative charge in OPN have been identified and named the polyAsp motif (poly-aspartic acid) and the ASARM motif (acidic serine- and aspartate-rich motif), with the latter sequence having multiple phosphorylation sites **(15).**

This overall negative charge of OPN, along with its specific acidic motifs and the fact that OPN is an intrinsically disordered protein allowing for open and flexible structures, permit OPN to bind strongly to calcium atoms available at crystal surfaces in various biominerals. Such binding of OPN to various types of calcium-based biominerals – such as calcium-phosphate mineral in bones and teeth, calcium-carbonate mineral in inner ear otoconia and avian eggshells,] and calcium-oxalate mineral in kidney stones – acts as a mineralization inhibitor by stabilizing transient mineral precursor phases and by binding directly to crystal surfaces, all of which regulate crystal growth **(16).**

Apoptosis:-

OPN is an important anti-apoptotic factor in many circumstances. OPN blocks the activation-induced cell death of macrophages and T cells as well as fibroblasts and endothelial cells exposed to harmful stimuli. OPN prevents non-programmed cell death in inflammatory colitis **(17).**

Bone remodeling:-

Osteopontin has been implicated as an important factor in bone remodeling. Specifically, OPN anchors osteoclasts to the surface of bones where it is immobilized by its mineral-binding properties allowing subsequent usage of its RGD motif for osteoclast integrin binding for cell attachment and migration **(18).**

OPN at bone surfaces is located in a thin organic layer, the so-called lamina limitans. The organic part of bone is about 20% of the dry weight, and counts in, other than osteopontin, collagen type I, osteocalcin, osteonectin, and alkaline phosphatase. Collagen type I counts for 90% of the protein mass. The inorganic part of bone is the mineral hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$. Loss of bone may lead to osteoporosis, as the bone is depleted for calcium if this is not supplied in the diet. OPN serves to initiate the process by which osteoclasts develop their ruffled borders to begin bone resorption **(18).**

Chemotaxis

OPN plays an important role in neutrophil recruitment in alcoholic liver disease. OPN is important for the migration of neutrophil in vitro. In addition, OPN recruits inflammatory cells to arthritis joints in the collagen-induced arthritis model of rheumatoid arthritis. OPN was also found to act as a macrophage chemotactic factor. In rhesus monkey, OPN prevents macrophages from leaving the accumulation site in brains, indicating an increased level of chemotaxis **(19).**

Clinical significance:-

OPN is expressed by different cell types of the immune system and regulates immunological response. It has been implicated in the pathogenesis of many autoimmune diseases as multiple sclerosis, rheumatoid arthritis, systemic lupus erythrematosis, Sjögren's disease, and inflammatory bowel diseases **(20).**

Also, being an inflammatory cytokine, OPN is found to be increased in atherosclerosis and cardiac diseases. Acute increase in OPN is protective, attenuate vascular calcification, and promote post ischemic neovascularization. In contrast, chronic increase in OPN is associated with an increased risk for major adverse cardiovascular events. OPN expression is considered a strong predictor of cardiovascular disease independent of traditional risk factors **(21).**

OPN has been suggested to play a role in several types of cancer, increased levels of circulating OPN and/or increased OPN expression by the tumor cells correlate with an unfavorable prognosis. OPN is expressed in benign and malignant thyroid tumors with increasing expression correlating with advancing malignancy **(22).**

Osteopontin as a biomarker in autoimmune diseases:-

Identifying a reliable biomarker is necessary for the diagnosis of autoimmune diseases and leads to early treatment of the disease. CSF and peripheral

blood levels of OPN can be used as diagnostic and prognostic biomarker in MS. Elevated levels of OPN are present in the CSF and peripheral blood of MS patients, reinforcing the evidence for the clinical utility of OPN as a promising biomarker for MS **(23).**

Circulating levels of OPN have been shown to be biomarkers of disease activity in the heterogeneous clinical setting of MS patients. Another study was conducted to identify markers and a specific inflammatory profile to differentiate between progressive and relapsing remitting multiple sclerosis (RRMS). They found that monocyte-associated OPN may be associated with PPMS. With regard to the role of OPN in SLE, The Koji et al. study showed that the N-half of the urinary OPN is reduced after treatment of lupus nephritis (LN), suggesting that the N-half of the urinary OPN could be a biomarker for assessing disease activity of LN **(10).**

They showed that urinary thrombin activity correlated with N-half concentration of OPN but not with OPN full concentration. These results suggest that N-half concentration of urinary OPN reflects renal inflammation. Therefore, N-half of urinary OPN could be a new disease activity marker for LN. In addition, it has been shown that serum concentration of OPN can be considered a renal injury in DN, without differentiating between active and remission. Moreover, another study provided new evidence for the link between OPN production with SLE progression and renal involvement. OPN may serve as a potential disease biomarker to monitor SLE disease severity and therapeutic efficacy **(10).**

Ostepontin and thyroid gland:-

Thyroid is an important endocrine gland and produces two main hormones thyroxine (T4) and tri-iodo thyronine (T3). Both of these hormones are under control of thyroid stimulating hormone (TSH) released by anterior pituitary gland and in turn it is controlled by thyrotrophin releasing hormone (TRH) of hypothalamus. The spectrum of thyroid dysfunction ranges from hypothyroidism (under production) to hyperthyroidism (over production). Thyroid disorders may affect individuals belonging to any age and gender **(24).** Most of the thyroid disorders remain undiagnosed as the clinical assessment alone is not sufficient enough to detect thyroid disorders so the biochemical tests are required to confirm the diagnosis. As a consequence there is still great interest in new biomarkers that complement existing diagnostic tools and may facilitate risk stratification in patients with thyroid disease.

OPN is expressed in benign and malignant thyroid tumors with increasing expression correlating with advancing malignancy. OPN is expressed in higher levels in papillary thyroid carcinoma and its expression levels were significantly associated with higher tumor size and presence of vascular invasion. OPN can be used as a biomarker in thyroid cancer, besides being a putative target for papillary thyroid cancer therapeutic approaches **(25).**

Thyroid hormone receptors are widely expressed in bone. Bone formation and turn over are greatly under the influence of thyroid hormones. T3 regulates chondrogenesis and bone mineralization, augments the synthesis of osteocalcin, collagen type 1, and increases proliferation, differentiation and apoptosis of osteoblasts. Hyperthyroidism leads to acceleration of bone turnover and loss of bone mineral density, while hypothyroidism leads to slowing of bone formation processes and in childhood causes growth retardation. Thyroid disorders have a great impact on the levels of bone turn over markers. Hyperthyroidism causes significant bone loss with higher levels of biochemical markers of bone turnover. OPN is considered one of the markers of bone turnover. OPN serum levels are negatively related to bone mineral density and positively correlated with bone turnover **(26).**

OPN is expressed in higher levels in papillary thyroid carcinoma and its expression levels were significantly associated with higher tumor size and presence of vascular invasion. OPN can be used as a biomarker in thyroid cancer, besides being a putative target for papillary thyroid cancer therapeutic approaches **(25).**

Hashimoto's thyroiditis is part of the spectrum of autoimmune thyroid diseases and is associated with various degrees of thyroid hypofunction and presents circulating antibodies to thyroid antigens; the incidence of Hashimoto's thyroiditis seems to be increasing in recent years. It is a disease of young and middle age and mostly occurs in females. Diffuse goiter and thyroid hypofunction were the common findings but can present an active phase of the disease that is transient with clinical manifestation of thyrotoxicosis. Nodules also represent an early stage of the disease. Evolution and destructive phases manifest with subclinical and overt hypothyroidism. It is the most common autoimmune thyroid disease and the most frequent cause of hypothyroidism **(27).**

Osteopontin has been reported to be up regulated in some people with hyperthyroidism and down regulated in hypothyroid patients, suggesting that it could be a novel marker in the identification of thyroid illnesses **(13).**

Large randomized controlled trials should be done to provide more definitive evidence for the role of OPN in patients with thyroid dysfunction. Further studies with larger sample size are required to compare OPN levels among patients with different etiologies of thyroid dysfunction.

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