**OSTEOPONTIN: A DIVERGENT PROTEIN MOLECULE**

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**ABSTRACT**

Osteopontin (OPN) is a phosphoglycoprotein having a multiple structural domain and diverse biological functions. OPN interacts with cell surface receptors through arginine-glycine-aspartate (RGD) and other many sticky domains that do not contain RGD. OPN has multiple role in different physiological circumstances including bone remodeling, immune modulation, inflammation, vascularisation and pathological conditions such as chronic inflammations, cardiovascular diseases, atherosclerosis, cancer and obesity. OPN has a wide range of biological functions depending on its structural changes and different environmental expression.

**INTRODUCTION**

 Osteopontin (OPN), otherwise known as Bone sialoprotein I (SPB I), Secreted phosphoprotein 1 (SPP 1), early T lymphocyte activation I (ETA I) or Urinary stone protein is a matricellular phosphoglycoprotein first described in 1971.1

 “Osteopontin” is derived from from the word “osteon” meaning bone and “pons” meaning bridge indicating its role as linking protein.2,3 OPN is expressed by a number of cells such as natural killer cells (NK cells), B and T cells, macrophages, neutrophils, dendritic cells, bone cells such as osteoblast and osteoclasts, epithelial cells of breast and neurons. OPN is found to be highly expressed in organs like bone, liver, brain, lung, adipose tissue, joints and body fluids such as saliva, human plasma, serum, urine and breast milk.4­

 OPN is extensively modified post translationally (phosphorylation, glycosylation, sulfation and proteolysis) by various cellular sources. As a result, OPN has a molecular weight range of 41 to 75 kDa and a structure and function that are cell type specific. OPN is an important part in several common physiological processes such as vascularization, immunological control, inflammation and bone remodeling.5

**STRUCTURE**

 The OPN gene, which has 7 exons and 6 introns, is found on human chromosome 4 region 22 (4q22.1).6 OPN has numerous cell sticky domains such as:

1. an arginin-glycine-aspartate (RGD) domain that engages in interactions with integrins on the cell surface such as αvβ3, αvβ1, αvβ5
2. SVVYGLR, a serine-valine-valine-tyrosine-glutamic acid-leucine-arginine compound containing domain interacts with α9β1 after being exposed by thrombin cleavage
3. the calcium binding domain (aa-216-228)
4. heparin-binding domain.7,8

OPN also interacts with CD44, areceptor for hyaluronic acid.9 The N-terminal and C-terminal zones are the two terminal zones of OPN. While the N-terminal contains integrin receptor binding zones, the C-terminal binds two heparin molecules as well as several forms of CD44.10 OPN belongs to the SIBLING (small integrin-binding ligand N-linked glycoprotein) family of proteins. Dentin matrix protein 1 (DMP1), dentin sialophosphoprotein (DSPP), integrin-binding sialoprotein (IBSP) and matrix extracellular phosphoglycoprotein (MEPE) are the other four members of this family.11,12



 **Fig: Structure of OPN showing its functional domains9**

**OPN ISOFORMS**

 A single SPP1 mRNA transcript is alternatively spliced to produce 5 OPN isoforms in humans. 1) complete OPN, commonly referred to as OPNa - 314aa, 2) OPNb, which is deficient in exon 5 (300aa), 3) OPNc, which is deficient in exon 4 (287aa), 4) OPN4, which is deficient in exons 4 and 5 (273aa), and 5) OPN5, which has an extra exon (327aa).13

**REGULATION**

 Several substances, including as hormones (such as vitamin D3 and estrogen), cytokines, and growth factors, have an impact on OPN expression. Through the activation of protein kinase C, inflammatory mediators and growth factors like interleukin-1 (IL-1), tumor necrosis factor (TNF), and platelet-derived growth factor (PDGF) drive OPN transcription.12(a)Steroids, retinoic acid, and glucocorticosteroids, in particular the seco-steroid hormone vitamin D3, stimulate OPN expression in bone cells, and a considerable reduction of OPN mRNA expression is seen in vitamin D3 deficiency. Cytokines, such as interleukin (IL)-1 and IL-6, also regulate OPN expression; (b)Increased transcription of the OPN gene, which is controlled by transactivation of cis-acting regions in the gene promoter, is linked to increased expression of OPN.14

**FUNCTION**

 Through a variety of pathways, osteopontin is critical for inflammatory response, biomineralization, wound healing, cardiovascular disease, cellular survival, cancer, and diabetes.

 **Fig:Important biological functions of OPN15**

**OPN IN INFLAMMATION**

 Numerous immune cells, including macrophages, neutrophils, dendritic cells, T and B cells, and microglia, express OPN. It functions as an adhesive protein to keep cells at the site and as a chemotactic molecule that facilitates the migration of inflammatory cells when there is inflammation. By promoting the expression of Th1 cytokines and matrix-degrading enzymes, OPN also has pro-inflammatory properties and may alter the immunological response.16 Several inflammatory disorders, including ulcerative colitis and Crohn's disease, have been found to be related with plasma OPN levels.17,18

**OPN IN BIOMINERALISATION**

 As one of the predominant non-collagenous proteins in bone, OPN is highly expressed in mineralized tissues including bone and teeth. Additionally, it is always present in pathological calcifications of soft tissues.7 OPN is found to be expressed by both osteoclast and osteoblasts. Osteoclast derived OPN inhibits hydroxyapatite formation leading to osteoporosis.1

 OPN is crucial for the formation of bone mass that is both neuron and endocrine mediated. By altering local bone remodeling via the β2-adrenergic receptor, the sympathetic nervous system regulates the bone mass. The mRNA and protein levels of OPN in plasma can increase, when the sympathetic nervous system is stimulated by isoproterenol. The production of cAMP by β2AR is controlled by OPN. Through the β2AR/cAMP signaling system, OPN thus contributes to the sympathetic nervous system's regulation of bone mass. Endocrine hormones, such as active vitamin D, Klotho, FGF23, and parathyroid hormone (PTH), are necessary for maintaining bone homeostasis. In the regulation of PTH, OPN plays a significant role.19

 OPN is also upregulated at areas of pathological calcification, such as cardiovascular calcification and urolithiasis.15

**OPN IN CARDIOVASCULAR DISEASES**

 OPN has been linked to the onset and progression of atherosclerosis, vascular remodeling, and restenosis since it is present at the site of atherosclerotic lesions together with macrophages and foam cells. OPN expression rises, as a result of mechanical insult to the endothelial lining. In an atherosclerotic lesion, the process of re-endothelializing a damaged endothelium lining is crucial for lowering thrombogenecity. By preventing endothelial cell migration and proliferation after damage, overexpression of OPN decreased re-endothelialization.20

 OPN also highly expressed in calcified atherosclerotic plaques. Along with pyrophosphates, fetuin-A and matrix glia protein (MGP), it is one of the significant negative regulators of calcification. OPN binds to hydroxyapatite firmly, which inhibits calcification directly.21 OPN is a strong inhibitor of vascular calcification, in contrast to its effect in inducing atherosclerotic inflammation.22

**OPN IN CANCER**

Local stromal cells that are involved in the early stages of the growth of tumor cells release OPN, which functions as a signal to draw in macrophages and perhaps also lymphocytes. While aberrant cells will be eliminated, this production of OPN offers defense against the cytotoxic byproducts of macrophages. However, transforming agents commonly stimulate OPN expression during the beginning and early stages of malignant growth. High-grade metastatic human gliomas exhibit strong OPN expression**.14**

Numerous malignancies, including lung23, breast24, prostate cancers25 have an overexpression of osteopontin mRNA and protein. Immunohistochemistry has discovered osteopontin expression in tumors, which is specifically localized in macrophages in some cancers and in both tumor cells and macrophages in other tumors.26

**OPN IN DIABETES**

 OPN is thought to have a significant role in the pathophysiology of diabetes and is regarded as a key factor in the development of insulin resistance and adipose tissue inflammation. In response to OPN production, pro-inflammatory cytokines rise, which is significant in the development of diabetes complications such nephropathy and vasculopathy. The level of OPN also increases in direct proportion to the severity of diabetes problems.27

 In autoimmune and chronic inflammatory diseases, OPN is only selectively expressed in neighboring inflammatory cells. It is also regarded as a sticky secreted molecule that controls the production of cytokines in T cells, dendritic cells, and macrophages as well as aids in the recruitment of monocytes and macrophages. Thus, it is claimed that OPN modulation of immune cell response is associated with a number of inflammatory disorders and may play a key role in the emergence of insulin resistance and inflammation of adipose tissue.28

**OPN IN OBESITY**

 Plasma OPN concentrations and body fat levels are correlated, and plasma OPN levels are much greater in overweight and obese people. OPN mRNA and protein have also been discovered to be expressed in omental adipose tissue, and this expression is raised in obesity and even higher in type 2 DM that is associated with obesity. And it is discovered that a minor diet-induced weight loss is accompanied by a considerable drop in plasma OPN levels.29

 Non-alcoholic fatty liver disease and obesity are frequently shown to be related. The level of hepatic steatosis-related OPN gene and its receptor CD44 expression in the liver was significantly elevated.1

**OPN IN LIVER DISEASES**

 OPN is an important cytokine that plays a role in the migration of non-parenchymal cells into necrotic areas of the liver and leads to fibrogenesis. OPN content in plasma has been shown to be a reliable indicator of liver fibrosis in a variety of liver abnormalities, including non-alcoholic steatohepatitis (NASH), alcoholic liver disease, viral hepatitis B (HBV), and viral hepatitis C (HCV).30,31 Additionally, plasma OPN is found to be raised in HCC and it has been reported as one of the most promising markers for HCC.32

**OPN IN RENAL DISEASES**

 Various renal diseases, such as the development of stones, tubulointerstitial nephritis, glomerulonephritis, acute ischemic renal damage, interstitial inflammation and fibrosis, hydronephrosis, lupus nephritis, and many others, are reported to have elevated OPN mRNA and protein expression. Furthermore, there is a strong correlation between this rise in OPN expression and proteinuria, a decrease in creatinine clearance, fibrosis, and the infiltration of macrophages and T cells.6

**CONCLUSION**

Osteopontin, a multifunctional protein is expressed by various cells of our body. It contributes to both pathogenesis of a number of disease situations, including as atherosclerosis, cancer, and other chronic inflammatory illnesses, as well as normal physiological functions. OPN is a potent inhibitor of vascular calcification as well as a significant regulator of biomernaralization. OPN contributes to a rise in macrophage and T cell numbers in the area of inflammation, which causes acute and chronic inflammatory disorders to become more inflammatory.

 A key molecule in field clinical research, osteopontin can be used as a target to better understand the etiology and prognosis of a number of disorders.

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