OSTEOPONTIN: A DIVERGENT PROTEIN MOLECULE

Abstract

Osteopontin (OPN) is a phosphoglycoprotein having a multiple structural domain and diverse biological functions. OPN interacts with receptors on cell surfaces 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 is involved in a variety of biological processes depending on its structural changes and different environmental expression.

KeyWords: Osteopontin, Inflammation, Cardiovascular diseases, Cancer, Diabetes, Obesity, Liver disease, Kidney disease

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I. 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 the word "osteon" meaning bone and "pons" meaning bridge indicating its function as linking protein.[2,3] OPN is expressed by numerous cells such as natural killer cells (NK cells), B and T cells, macrophages, polymorphonuclear leukocytes, dendritic cells, osteoblast, osteoclasts, epithelial cells of breast and nerve cells. 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 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]

II. 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 $\alpha_v\beta_3$, $\alpha_v\beta_1$, $\alpha_v\beta_5$

2. SVVYGLR (serine-valine-valine-tyrosine-glutamic acid-leucine-arginine) domain interacts with $\alpha_9\beta_1$ after being exposed by thrombin cleavage

3. the domain that binds calcium (aa-216-228)

4. heparin binding domain.[7,8]

OPN also interacts with CD44, areceptor for hyaluronic acid.[9] The N and C terminal 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), Integrin binding sialoprotein (IBSP), Matrix extracellular phosphoglycoprotein (MEPE) and Dentin sialophosphoprotein (DSPP) are the other four members of this family.[11,12]

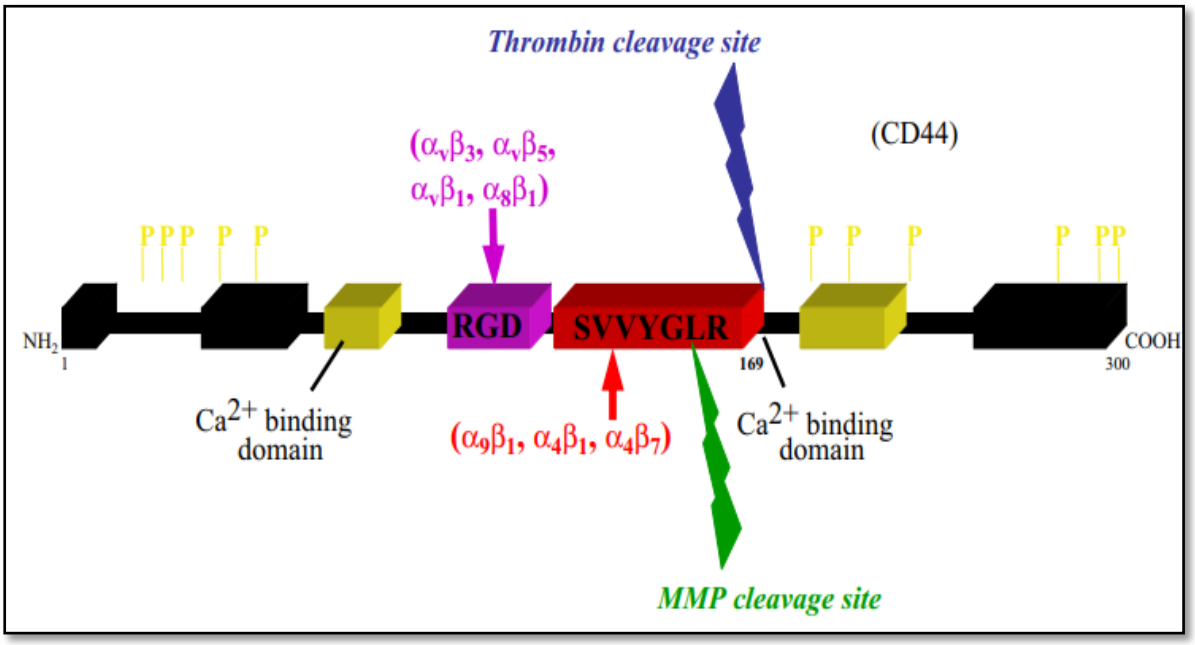

Figure 1: Structure of OPN Showing its Functional Domains[9]

III. 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 & 5 (273aa), and 5) OPN5, has an extra exon (327aa).[13]

IV. REGULATION

Several substances, including hormones (such as vit D3, estrogen), cytokines and growth factors have an impact on OPN expression. Through the activation of protein kinase C, interleukin-1 (IL-1), tumor necrosis factor (TNF) and platelet derived growth factor (PDGF) drive transcription of OPN.[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. (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]

V. FUNCTION

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

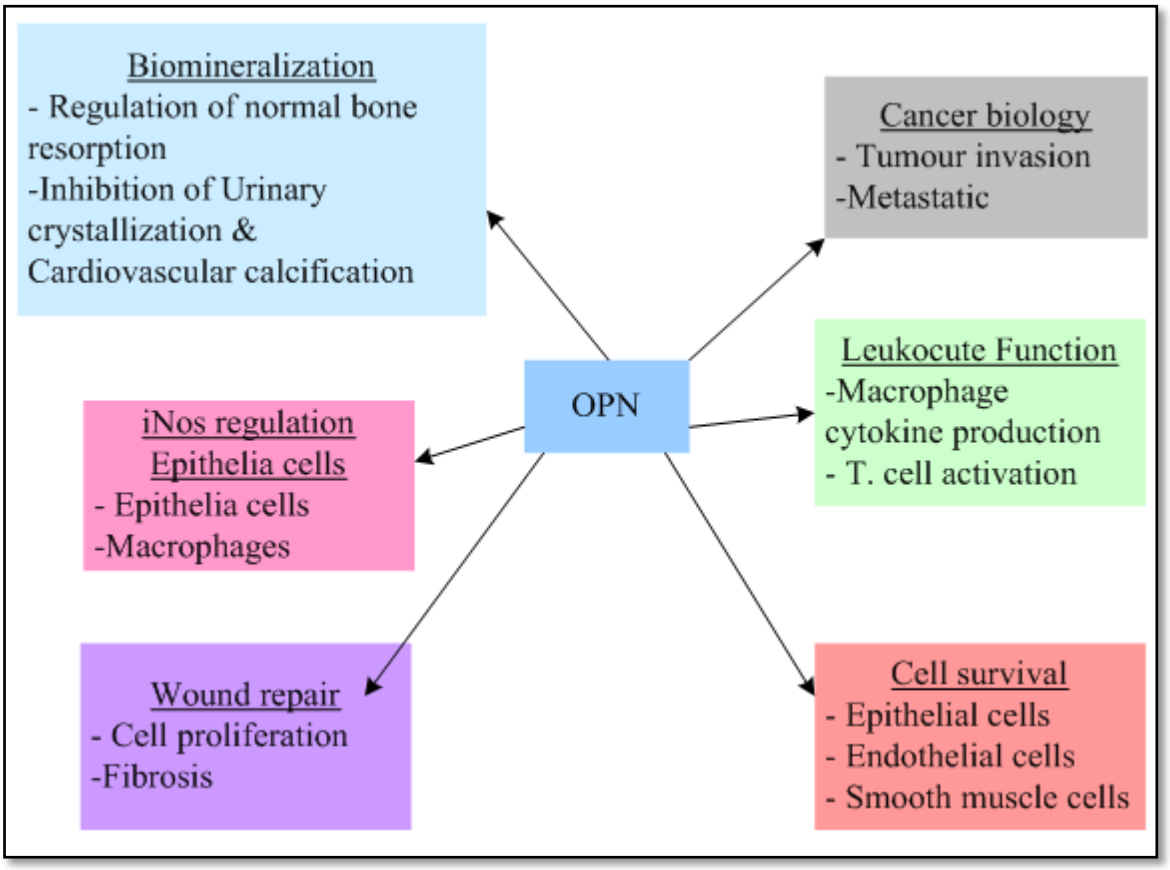

Figure 2: Important Biological Functions of OPN[15]

1. **OPN in Inflammation:** Numerous immune cells including macrophages, polymorphonuclear leukocytes, dendritic cells, T-cells, 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 diseases such as Ulcerative colitis and Crohn's disease, have been found to be related with plasma OPN levels.[17,18]

2. **OPN In Biomineralisation:** OPN is significantly expressed in mineralized tissues, such as bone and teeth, and is one of the main non-collagenous proteins in bone. 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 formation. 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]Also OPN expression is upregulated at areas of pathological calcification such as cardiovascular calcification and urolithiasis.[15]

3. **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, over expression of OPN decreased re-endothelialization.[20]

   Moreover, hardened atherosclerotic plaques exhibit significant expression of OPN. 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]

4. **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 lung[23], breast[24], prostate cancers[25] have an overexpression of osteopontin mRNA and protein. Immunohistochemistry has discovered osteopontin expression in tumors, which is specifically localized in macrophages in certain cancers and in both macrophages and cancerous cells in other tumors.[26]

5. **OPN in Diabetes:** OPN is thought to have a significant role in the pathophysiology of diabetes and is regarded as a contributory factor in the development of inflammation in adipose tissue and insulin resistance In response to OPN production, pro inflammatory cytokines rises, 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 chronic inflammatory and autoimmune 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 various inflammatory conditions and may play a key role in the emergence of insulin resistance and inflammation of adipose tissue.[28]

6. **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 adipose tissue in omentum, 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 OPN levels in plasma.[29]

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

7. **OPN in Liver Diseases:** OPN is a significant cytokine that aids in non-parenchymal cells migration into necrotic areas of liver and lead 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]

8. **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]

VI. 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 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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