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The Biochemistry, Functions, And Clinical Importance of Osteopontin: A Review

Wafaa Mohammed Ridha Abdel Rasoul
The General Directorate of Education in Najaf Al-Ashraf, Iraq

Mariam Akeel Al-Taee
Department of biology, College of Science, University of Kerbala 56001, Iraq

Hanaa Mumtaz Hussein
The General Directorate of Education in Najaf Al-Ashraf, Iraq

Ali A. Al-fahham
Faculty of Nursing, University of Kufa, Iraq

Corresponding Author - Ali A. Al-fahham

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Abstract

Osteopontin (OPN), a pleiotropic matricellular glycoprotein, has been recognized as an important molecule at the crossroads between biochemistry and mechanisms of disease. Structurally complex, many isoforms and extensive post-translational modification (PTM), OPN serves as a modulator of cell adhesion, mobility, immune signalling and the extracellular matrix. These properties permit it to be involved in physiologic functions like bone mineralization, wound repair, and host defense. Nevertheless, abnormal OPN expression or dysregulation causes chronic inflammation, fibrosis, cardiac remodeling and metabolic disorders as well as cancer development. The higher systemic and tissue levels of OPN have been proven to be potential biomarkers associated with the severity and prognosis in different clinical setting, however bioassay variation and context-dependent functions remain controversial. Interest for OPN goes beyond diagnostics: clinical trials targeting it with emphasis on selectively inhibiting its isoforms and signal transduction pathways are currently being conducted. The objective of this review is to discuss the biochemistry, etiological roles, and clinical relevance based on current understanding of OPN and its translational application in contemporary medicine.

Keywords: Osteopontin, Bone Mineralization, Wound Healing, Host Defense.

Introduction

Osteopontin (OPN; also known as SPP1) is a well conserved and multifunctional matricellular protein that resides at the intersection between extracellular matrix (ECM) and cellular signaling networks. At the most general level, matricellular proteins are not structural in nature but instead play multifaceted roles in modulating cell–matrix interactions, cell migration behaviors and intercellular signaling processes; OPN is unique among these by functioning concurrently as an adhesion substrate, cytokine-like signaling molecule and mineralization inhibitor. This wide spectrum of function(s) most probably accounts for why OPN has

garnered so much interest in diverse biomedical areas – from skeletal biology to immunity, cardiology, metabolism, and tumor biology – as it becomes increasingly scrutinized both as a mechanism mediator of disease and as a potential clinical biomarker (Icer & Gezmen-Karadag, 2018; Lin et al., 2022).

Zooming in on its molecular identity, OPN is a highly post-translationally modified, acidic phosphoglycoprotein that exists in multiple isoforms and locations. Secreted OPN (sOPN) interacts with integrins and CD44 splice variants via defined adhesion motifs (e.g., RGD sequence), modulating cell adhesion, migration, and survival signaling. Concomitantly, OPN intracellular variants (OPN-i) with differential functionality, e.g., in immune cell homeostasis and signal transduction, have been reported, clearly indicating that OPN's biology is not a single external activity. PTMs including proteolytic cleavage, glycosylation and phosphorylation serve to significantly expand OPN's receptor affinities and downstream effects that tissues are able to tap into in a context-dependent "toolbox" of actions during development, repair and pathological remodeling (Leavenworth et al., 2015; Lin et al., 2022).

OPN acts as a molecular conductor of injury, inflammation and repair from the pathogenic side. It is induced early upon tissue injury, infection or mechanical stress and takes part in leukocyte recruitment, cytokine regulation and extracellular matrix remodeling. As a result of being key in numerous chronic diseases, abnormal OPN expression or isoform balance could be causal rather than just coincidental to pathogenesis. Experimental animal models and human studies have identified OPN in atherosclerosis, myocardial remodeling, chronic kidney disease, metabolic inflammation and fibrosis disorders where it commonly mediates maladaptive matrix remodeling and chronic inflammatory response (Shirakawa et al., 2021; Zhao et al., 2024).

In oncology, OPN's pleiotropic activities are co-opted by tumors to promote proliferation, angiogenesis, immune evasion, and metastatic dissemination. Elevated OPN expression in tumor cells and tumor-associated stroma has been associated with more aggressive phenotypes and poorer clinical outcomes in multiple cancers. Mechanistic studies implicate OPN in epithelial–mesenchymal transition, cancer stemness, and the reprogramming of tumor-infiltrating immune cells toward pro-tumor phenotypes. These insights position OPN not only as a prognostic biomarker but also as a potential therapeutic target in settings where OPN drives recurrence or therapy resistance (Gu et al., 2024; Wei et al., 2017).

Clinical attentions of OPN are claimed as circulation/tissue biomarker in many specialities. Serum/ plasma OPN molecules have been studied for risk stratification and disease monitoring in CVR, metabolic syndrome & diabetes, chronic inflammatory conditions and various malignancies. Although numerous studies demonstrate that increased OPN associates with disease severity, prognosis, or adverse remodeling, assay heterogeneity and isoform complexity as well as comorbid inflammatory states interfere with straightforward clinical translation. Accordingly, a critical question in the current era is how best to differentiate context-dependent OPN signals that are causally important from non-specific inflammation-related elevation of circulating levels of OPN (Shirakawa et al., 2021; Zhao et al., 2024).

The translational optimism surrounding therapeutic modulation of OPN is supported by both mechanistic plausibility and an ever-growing body of clinical association data. Inhibiting OPN-induced pathways (eg, integrin ligation, CD44 interactions or specific splice variants) provides a potential therapeutic handle to mitigate fibrosis, control tumour progression or attenuate maladaptive cardiac remodelling. But because OPN functions are complex, protective in some settings (e.g., acute wound healing, host defense) and pathogenic in others–simply shutting it down, without an understanding of such isoform- and tissue-specific roles, is unwise. Recent preclinical and early clinical studies therefore stress the need for selective modulation strategies and better biomarkers to identify patients most likely to benefit (Gu et al., 2024; Zhao et al., 2024).

Osteopontin between biochemistry and disease mechanisms

Osteopontin (OPN) is a highly phosphorylated glycoprotein with strong affinity for integrins, and it has been identified as an essential mediator in numerous physiological and pathological processes, including bone mineralization, metastatic progression of tumors, inflammatory reactions, immune regulation, and cellular survival mechanisms. Osteopontin (OPN), a multifunctional extracellular protein, participates in

numerous pathological and physiological processes, such as immune modulation, cytokine signaling, tissue mineralization, inflammatory responses, and tumorigenesis. The structural configuration and functional properties of OPN are strongly modulated by post-translational modifications (PTMs). However, a detailed, site-specific characterization of O-glycosylation within human OPN has not yet been reported. In this study, we investigated the global glycan profile of recombinant human OPN using a lectin array and performed in-depth structural characterization of O-glycopeptides via mass spectrometry (MS). MS^3 spectra of the O-glycopeptides provided backbone cleavages, enabling precise peptide sequence determination. Additionally, 26 phosphorylation sites were mapped through reverse-phase liquid chromatography–tandem mass spectrometry (RPLC-MS/MS), including a novel phosphorylation site at Y209. Collectively, this work presents a comprehensive, site-specific structural analysis of OPN O-glycosylation and identifies its phosphorylation sites (Icer & Gezmen-Karadag, 2018).

Biochemical Characteristics of Osteopontin

Osteopontin (OPN), alternatively named secreted phosphoprotein-1 (SPP1), sialoprotein-1, or early T lymphocyte activation-1 (Eta-1), belongs to the small integrin-binding ligand N-linked glycoprotein (SIBLING) family. This group consists of non-collagenous proteins (NCPs) that are predominantly localized within mineralized tissues, such as bone and dentin, where they perform essential functions in bone metabolism. This includes the SIBLING family members, MEPE (matrix extracellular phosphoglycoprotein), DSPP (dentin sialophosphoprotein), DMP1 (dentin matrix protein 1) and BSP/IBSP (bone sialoprotein). These secreted soluble glycoproteins undergo multiple posttranslational modifications, including alternative splicing, phosphorylation, glycosylation and proteolytic cleavage to perform their biological functions. SIBLINGs act as autocrine and paracrine regulators and functionally interact with cell-surface integrins through their domains (Lin et al., 2022).

OPN is the most well-studied member of this family. Discovered by Senger in 1979 as a 60-kDa secreted transformation-specific phosphorylated protein, it is classified as a multispecific extracellular matrix-associated glycoprotein. RGD motif and its molecular weight appears to be 34-75 kDa due to posttranslational modifications. Furthermore, it contains an approximately 314 amino acids length GRGDS in-sequence, which promotes interaction on integrin receptors involved in cellular responses. The SPP1 gene, which encodes OPN, is located on the long arm of chromosome 4 in tandem repeat and generates three alternatively spliced isoforms: OPN-A, OPN-B and OPN-C. Of these, OPN-A is the complete length isoform (Rezaee et al., 2020).

MAPKs are activated in response to diverse extracellular and intracellular stimuli in mammalian cells. In the traditional signaling pathway stimulaIntroduced at membrane-bound receptors through this and traverses the cytoplasm (via MAPK) to activate nuclear targets. MAPKs function as nuclear transcriptional regulators, which govern a broad array of cellular functions including the activation of proinflammatory responses to bacterial challenge. The combined activation of several signaling pathways demonstrated the pleiotropic and redundant regulation from OPN as OS in miscellaneous tissues (Shirakawa et al., 2021).

Osteopontin in Inflammation and Immunity

Osteopontin (OPN) is a known multifunctional protein and plays a critical role in bone remodeling and immune regulation. It is not only expressed in osteogenic cells but also many types of immune cells, such as DC, neutrophils, macrophages, natural killer (NK) cells, natural killer T (NKT) cells and B and T lymphocytes (Zhao et al., 2024). OPN is an important regulator of T-helper (Th) cell subsets and the induction of immune responses against a wide variety of pathogens. In vitro studies showed that parasite-infected activated murine macrophages secreted OPN protein, and that mice with acute infection had higher blood OPN levels during maximal parasitemia. Treatment of newly infected mice with neutralizing anti-OPN antibody led to decreased Th1 and Th17 responses, enhanced parasitemia and early death compared with non-immune IgG treated group. Furthermore, anti-OPN treatment reduced circulating levels of IgG2a antibodies, IL-17A, IFN-γ and IL-12 p70. Furthermore, ex vivo splenic macrophages and $CD4^+$ T cells from anti-OPN treated animals synthesized less IL-17A, IFN-γ and IL-12 p70 and more IL-10. OPN - α(v) - Th1 Interactions between OPN and α(v)β(3) integrin were important for the induction of suppressive cytokine production (IL-10 suppression) while the interaction between OPN and its HLCR CD44 was found to be critical

for inflammation (Th17).These amplificatory effects on immune function place OPN as both a potential marker of disease severity in autoimmune processes as well as a novel therapeutic option (Shirakawa et al., 2021).

Osteopontin in Cardiovascular and Metabolic Disorders

Osteopontin (OPN) is expressed to a great extent in cardiovascular structures after myocardial infarction, vascular injury and during heart failure development. Increased expression of this protein in VSMC and macrophages promotes remodeling of extracellular matrix, vascular calcification, and fibrotic scar. Short term elevation of OPN may help tissue repair and wound healing post-cardiac injury, however persistent increase in its expression often correlates with a maladaptive remodeling, excessive myocardial fibrosis and reduced survival of HF patients (Shirakawa et al., 2021).

Similar torrents are taking place in metabolic disorders like obesity and T2DM. In such conditions, OPN is over-expressed from adipose tissue and infiltrating immune cells. OPN recruits and polarizes macrophages to proinflammatory subtypes, this manner of development establishes the mechanism between obesity-related inflammation and insulin resistance (Icer & Gezmen-Karadag, 2018). Higher levels of circulating OPN in MetS patients underscore the potential value of assessing this measure for cardiometabolic risk profile (Wei et al., 2017).

Osteopontin in Fibrosis

Another prominent area of pathogenic OPN biochemistry is in the context of fibrotic disease. OPN stimulates fibroblast proliferation, myofibroblast differentiation and excess synthesis of extracellular matrix proteins, such as collagen. This is shown in chronic kidney, pulmonary and hepatic fibrosis where OPN levels correlate not only with the severity of disease but also play a role in the process of fibrogenesis. Given that fibrosis represents a final common pathway in many chronic diseases, OPN emerges as a single molecule mediator connecting the biochemistry of matrix regulation to clinical progression from injury to organ failure (Rezaee et al., 2020).

Osteopontin in Cancer

The role of OPN in cancer is one of the most investigated fields in OPN biology. OPN is often expressed at high levels in both tumors and tumor-related stroma; here, it has been observed to promote metastasis, epithelial–mesenchymal transition (EMT), angiogenesis, and tumor growth (Gu et al., 2024). OPN binds integrins and CD44 to initiate survival and invasive signals in cancer cells. Furthermore, OPN reprograms the tumor milieu through immune cell infiltration modulation to create immunosuppressive phenotypes which contribute to tumor immune escape. Clinically, high plasma level or intratumoral expression of osteopontin (OPN) has been associated with advanced stages of the disease, poor outcome, and resistance to treatment in several cancers, including breast, lung, prostate and colorectal cancer. These findings have inspired studies of the potential role of OPN as prognostic biomarker and a therapeutic target to inhibit pathways that drive tumor growth and progression (Wei et al., 2017).

Molecular Regulation of Osteopontin

Transcriptional regulation The gene-expression of osteopontin (OPN) is mainly controlled at the level of transcription from the SPP1-gene and several isoforms generated by alternative splicing has been identified, including OPNa, OPNb and OPNc. OPNa includes exons 2–7, and OPNb and OPNc lack exons 5 and 4, respectively. In spite of this structural diversity, the signal sequence is conserved among all human splice variants and protects the important protein domains (i.e. calcium binding region, thrombin binding sites). Conserved motifs common in the isoformsvare SVYGLR and RGD, as well as cleavage sites for matrix metalloproteases (MMPs). In the absence of translation of the signal sequence, intracellular OPN (iOPN) is formed; its inclusion and cotranslational translocation give rise to secreted OPN (sOPN). OPN by alternative splicing and translational initiation has a variety of isoforms that are responsible for its structural heterogeneity and functions. These isoform differences, in turn, result in alterations to post-translational modifications, proteolytic susceptibility and receptor binding. As a result, some isoforms have no integrin binding and therefore affect the effect of cells adhesion and signal transduction; OPN can be involved in many other biological processes, in a tissue- or context-dependent way (Karasalih et al., 2025).

Transcriptional Regulation

Multiple OPN isoforms are generated through alternative splicing and translation initiation. In humans,

alternative splicing gives rise to OPNa, OPNb, and OPNc. OPNa contains exons 2–7, representing the complete protein-coding sequence, whereas OPNb and OPNc lack exons 5 and 4, respectively. All human splice variants retain the signal sequence necessary for secretion and conserve essential domains, including calcium- and heparin-binding regions, cleavage sites for thrombin and matrix metalloproteases (MMPs), and motifs such as SVVYGLR and RGD. These isoforms have been extensively characterized, particularly in cancer research.

Alternative translation initiation results in intracellular OPN (iOPN) when the signal sequence is omitted, preventing secretion, whereas inclusion of the signal sequence produces secreted OPN (sOPN). Both human and mouse OPN have been localized to the cytoplasm and nucleus, although the functional consequences of the iOPN-to-sOPN ratio have been minimally explored in human disease. Importantly, iOPN and sOPN exhibit distinct phosphorylation and glycosylation patterns, reflecting their divergent subcellular localizations and functional roles (Jia et al., 2025).

It was found that enhanced expression of the OPN gene was observed in the kidneys of the hyperglycemic SUR1-E1506K mouse model. The glucose-induced increase in OPN transcription was strongly correlated with enrichment of activating histone modifications, including H3K9ac, H3K4me1, and H3K4me3, together with a concurrent reduction in the repressive histone mark H3K27me3 at the OPN promoter. Parallel findings were obtained in human mesangial cells exposed to elevated glucose concentrations. Additional evidence was provided by pharmacological modulation of histone remodeling: inhibition of histone deacetylases with trichostatin A and blockade of histone methyltransferases with MM-102 both influenced OPN expression levels (Cai et al., 2016).

Post-Transcriptional Modulation

Osteopontin (OPN) is an extracellular glycosylated phosphoprotein that facilitates cell adhesion through interactions with multiple integrin receptors. Previous studies demonstrated that an OPN mutant lacking five O-glycosylation sites (Thr134, Thr138, Thr143, Thr147, Thr152) within the threonine/proline-rich region exhibited increased cell adhesion and phosphorylation compared with the wild-type protein. Nevertheless, the precise role of O-glycosylation in modulating OPN's adhesion and phosphorylation remains unclear. In this study, we show that site-specific O-glycosylation within the threonine/proline-rich region can influence OPN's cell adhesion and phosphorylation either independently or synergistically (Lin et al., 2022). Using site-directed mutagenesis, we observed that OPN mutants with substitutions at Thr134/Thr138 exhibited reduced adhesion, whereas mutations at Thr143/Thr147/Thr152 enhanced adhesion. Single-site mutations, however, did not affect cell adhesion. Functional adhesion assays using blocking antibodies against αvβ3 and β1 integrins, as well as αvβ3-overexpressing A549 cells, indicated that site-specific O-glycosylation modulates OPN's interaction with these integrins. Phosphorylation analyses via Phos-tag and LC-MS/MS revealed that phosphorylation levels and sites were influenced by O-glycosylation status, although the total number of O-glycosylation sites did not correlate directly with phosphorylation levels. Furthermore, correlation analysis showed that phosphorylation levels and cell adhesion activity in site-specific O-glycosylation mutants were not consistently aligned (Rezaee et al., 2020).

Receptor Interactions and Signaling

Osteopontin (OPN) and splice variants of CD44 (CD44(V)) have been identified as biomarkers of tumor progression. In human gastric cancer, both OPN and CD44(V) are frequently overexpressed, and ligation of CD44(V) by OPN has been shown to enhance cell survival through integrin-mediated signaling. Cellular resistance to UV-induced apoptosis was increased following OPN treatment, and this anti-apoptotic effect was dependent on the presence of CD44 isoforms containing variant exons V6 or V7. These findings were confirmed by overexpressing individual CD44(V) isoforms in AZ521 gastric cells with minimal endogenous CD44 expression and by knocking down V6-containing CD44 in HT29 colon cells. Although OPN is capable of interacting with RGD integrins, the RGD motif was found to be non-essential for its anti-apoptotic activity.

The observed cytoprotective effect of OPN was primarily mediated through engagement of CD44(V) and the subsequent activation of inside-out signaling via Src, resulting in robust integrin activation (Icer & Gezmen-Karadag, 2018; Zhao et al., 2024). Furthermore, OPN-induced anti-apoptosis was observed when cells were

cultured on fibronectin but not on poly-D-lysine. Interference with integrin–extracellular matrix interactions, either by application of an anti-integrin β1 antibody or by expression of dominant-negative focal adhesion kinase to block ECM-derived signaling, abolished OPN-mediated cell survival (Leavenworth et al., 2015).

Conclusion

Osteopontin (OPN), a matricellular glycoprotein now recognized as a multifunctional player, stands at the crossroads between biochemistry and pathology. Being structurally heterogenous as a result of various isoforms, and extensive post-translational modificationtions, it regulates cell adhesion, motility, immune responses and remodelling of the ECM. These properties allow it to play a role in biologic function including bone metabolism, wound repair and host defense. Nevertheless, because the abnormal expression or activation of OPN is associated with chronic inflammation, fibrosis, cardiovascular remodeling, metabolic disease process and tumorigenesis. High circulatory and tissue concentrations of OPN have been evaluated for disease severity and prognostication in clinical settings, although the context dependability of these measurements is challenged by assay variability and specialized roles. OPN not only holds diagnostic potential, it is also a therapeutic target and approaches for therapeutic development targeting selective OPN isoforms and signaling pathways are presently being studied. This review summarizes current knowledge of OPN's biochemistry, etiological roles, and clinical relevance, highlighting its translational potential in modern medicine.

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