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Osteopontin expression in dermatological disorders

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Abstract
Osteopontin (OPN) is a multifunctional protein that plays a role in a wide range of physiological functions, including wound healing, inflammatory reactions (especially autoimmune ones), and fibrotic disorders. Multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune disorders are associated with elevated OPN levels. One way that OPN helps psoriasis is by encouraging the development of new blood vessels, which in turn facilitates the entry of inflammatory cells. One of the most frequent T-cell-mediated diseases, allergic contact dermatitis, is controlled by OPN. It appears that OPN plays a crucial role in granuloma formation by recruiting macrophages.

Keywords: Osteopontin (OPN), multifunctional protein, wound healing, inflammatory reactions

Introduction
The first identification of osteopontin (OPN), a glycoprotein, in osteoblasts occurred in 1986. This protein serves multiple purposes and is widely distributed in bone. The protein has 314 amino acids, a high concentration of serine, glutamate, and aspartate residues, and functional domains that allow it to bind calcium [1].

The tissue microenvironment, other molecules present, and the engagement of particular receptors can all impact how OPN is effective. While OPN is involved in tissue homeostasis and repair under normal physiological circumstances, it may participate in disease development in pathological states like inflammation or cancer when expression is high. As an example, OPN plays a crucial role in apoptosis regulation by acting as an anti-apoptotic factor and protecting macrophages, T cells, fibroblasts, and endothelial cells from damaging stimuli that could otherwise trigger programmed cell death [2].

Patients with systemic lupus erythematosus, allergic contact dermatitis, psoriasis, alopecia areata, and high OPN levels may have a role in the development of these conditions [1].

Osteopontin
Osteopontin (OPN) is a glycol protein that contains phosphorylated acids and is biologically involved in the regulation of the immune system and bone remodeling. "Osteo" meaning "bone" and "pontin" meaning "bridge" are the two parts of the compound that make up the name osteopontin. Despite its initial isolation from bone as a glycosylated phosphoprotein rich in sialic acid, it was later discovered to have a broader distribution. In contrast to its low expression in healthy tissues, OPN shows stunning upregulation in inflammatory and tissue remodeling sites. [3].

Structure of Osteopontin
The 314 amino acid glycophosphoprotein osteopontin contains both O- and N-linked oligosaccharides in addition to its abundance of aspartic acid and other acidic properties. It contains five distinct binding regions: one for arginine, glycine, and aspartic acid; two for heparin; one for thrombin; and one for calcium [4].

Additional proteins associated with OPN include matrix metalloproteases 3 and 7. To interact with different integrin receptors, OPN has two crucial regions: arginine-glycine-aspartic acid (RGD) and serine-valine-valinetyrosine-glutamate-leucine-arginine (SVVYGLR). MMP-2, MMP-3, MMP-7, and MMP-9 all use OPN as a substrate [4].

Osteopontin Receptors

Through specific-binding motifs, osteopontin binds to cell surface receptors.:

- **Integrins receptors:** Osteopontin binds to integrin family proteins. Both cancer cells and other types of stromal cells express receptors from the integrin family. Most of OPN's interactions with integrins take place in the RGD region. Integrin αvβ3 is an OPN receptor that has been extensively studied and is known to promote tumor growth and metastasis. Through its association with OPN, αvβ3 integrin also facilitates the migration of breast cancer cells. [5].
- **CD44 receptors:** Osteopontin regulates multiple cellular processes via its C-terminal region interactions with the hyaluronate receptor, CD44. The many CD44 receptors expressed by cancer cells are produced by alternative splicing of a single gene. Cell migration is improved when OPN binds to CD44 with the help of β1-integrin. [6].

Physiological expression of osteopontin in skin

The basal keratinocyte layer showed OPN expression when normal skin was stained. In addition, sebaceous glands, sweat glands, and hair follicles all express OPN. In sun-exposed skin, OPN is most noticeable in the spinous cell layer and becomes increasingly intense as it moves towards the granular cell layer. [7].

Osteopontin in dermatology

1. Osteopontin and Autoimmune Diseases

Multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), and other autoimmune disorders are associated with elevated OPN levels. OPN's detrimental effects in autoimmune diseases may be attributed to its capacity to stimulate the secretion of IL-17 and IFN-γ in T cells and IL-6 in monocytes, as well as to inhibit activation-induced cell death, which is involved in the termination of the immune response. Additionally, OPN may promote lymphocyte adhesion and migration [8].

2. Osteopontin in psoriasis

In psoriasis, OPN promotes the development of blood vessels, which in turn aids the infiltration of inflammatory cells. This process is mediated by IL-1 and matrix metalloproteinase-9, which are both activated by OPN and TNF-α. There may be a connection between OPN expression and its Th1/Th17 skewing effects in various autoimmune disorders, as indicated by the elevated plasma levels of OPN and its powerful expression in psoriatic lesions [9].

The production of osteopontin in lymph nodes improves the antigen-presenting capability of dendritic cells (DC) and Langerhans cells (LC) in lymph nodes after injury. The inflammatory Th1 response is stabilized when DC encounters OPN, which activates and polarizes LC and mDC towards a Th1 phenotype. At the same time, effector T cells can be directly induced to produce sOPN by superantigens. Consequently, more immune cells are attracted to the inflamed areas by the chemotactic sOPN [10].

Osteopontin can block apoptosis, which means it can prolong inflammation and promote keratinocyte proliferation. Moreover, OPN enhances Th-17 polarizing mDC function by preventing IL-27 expression. The development of psoriasis is greatly influenced by other cytokines, including IL-23 and TNF-α, so it is crucial to establish a connection between OPN and these other factors. The β3 integrin receptor may be the direct pathway by which more OPN induces IL-17 production by CD4+ T cells [10].

3. Osteopontin in lichen planus

Oral lichen planus (OLP) patients recently had an overexpression of OPN, which may indicate a link between this protein and the various clinical forms of OLP. T cell subpopulations' migration and recruitment to the inflammation site are regulated by particular cell surface molecules. The most well-studied of the several OPN receptors is CD44, which is involved in mediate cell chemotaxis and attachment in addition to its significant functions in lymphocyte activation, migration, proliferation, and expansion[11].

Liu *et al.* found that OPN levels in the plasma are significantly higher than normal, suggesting that this may be the cause of CD44 overexpression in OLP patients [12].

4. Osteopontin in immunobullous dermatoses

Elevated levels of circulating autoantibodies were associated with greater serum levels of osteopontin (OPN), especially in patients with both oral and cutaneous pemphigus [13].

The autoimmune disease pemphigus has no certain cure and might be fatal. The rise in OPN levels seen in pemphigus patients raises the possibility that OPN plays a role in the etiology of pemphigus and could be a valuable treatment target for this disease [14].

5. Role of osteopontin in allergic contact dermatitis

One typical T-cell-mediated illness that OPN regulates is allergic contact dermatitis. Through CD44 and αv integrins, secreted OPN plays a role in the emigration of LC/DC from the epidermis and draws them to lymph nodes that drain the skin. Crucially, by secreting TNF-α and IL-12, sOPN causes DC to become more inflammatory, which in turn polarizes DC towards a Th1-skewing phenotype [15].

6. Role of osteopontin in immediate type allergy

Additionally, secreted OPN has been suggested to play a role in the control of Th2-mediated allergic illness, which occurs when treatment for immediate-type allergies distorts the human immune system, by acting differentially on pDC and mD [16].

7. Osteopontin and infection

By stimulating type-1 T helper cell-mediated immunological responses and granuloma formation by promoting IL-12 production by macrophages, osteopontin is an important component of the immune system's defense mechanisms against pathogenic microbes. Viral antigens can produce osteopontin by ligating toll-like receptors. A strong Th1 cell response is produced as a result of intracellular OPN enhancing IFN-α expression. Microbiological, allergy, and autoimmune skin diseases are influenced by these complex regulatory roles of OPN [16].

8. Osteopontin in granulomatous diseases of the skin

One particular cell-mediated response to infections caused by microorganisms like Mycobacteria is the formation of granulomas. It appears that OPN plays a crucial role in

granuloma formation by recruiting macrophages. Macrophages are substantially stimulated to express OPN by the cytokine TNF-α, which plays a crucial role in the formation of granulomas. One possible explanation for the ability of anti-TNF-α antibodies to treat sarcoidosis is the down- modulation of OPN expression that occurs after TNF-α depletion. [16].

9. Osteopontin in skin tumor progression

Tumor thickness, invasiveness, and mitotic index were all observed to be correlated with OPN staining in primary melanoma. Both disease-specific and recurrence-free survival were negatively linked with higher tumor OPN. The metastases to sentinel lymph nodes was also substantially related with OPN. These studies all point to the importance of OPN in melanoma development when taken collectively [17].

OPN is expressed in squamous cell carcinomas and actinic keratosis, but it is either not expressed at all or expressed at very low levels in tumors that do not have the capacity to metastasize such as solid basal cell carcinomas [17].

Conflict of Interest

Not available

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Not available

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