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The role of osteopontin in skin diseases

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Abstract

Osteopontin, a glycoprotein, was first identified in 1986 in osteoblasts. It is a multifunctional protein, highly expressed in bone. It has many functions on bone mineralization, regulation of immune cell function, inhibition of calcification, control of tumor cell phenotype and cell activation. Osteopontin has been involved in the pathogenesis of many skin diseases as systemic lupus erythematosus, infection, psoriasis, contact dermatitis and cancer. Some of these diseases are discussed in this review.

Introduction

Osteopontin (OPN), a glycoprotein was first identified in 1986 in osteoblasts. It is a multifunctional protein, highly expressed in bone [1]. Osteopontin is also known as bone sialo protein I (BSPI), early T-lymphocyte activation (ETA-I), Urinary stone protein, Nephropontin, Uropontin secreted phosphoprotein 1(SPP 1) and Rickettisia resistance (Ric) 44 K BPP (bone phosphoprotein). Osteopontin has a defined role in bone mineralization, regulation of immune cell function, inhibition of calcification, control of tumor cell phenotype and cell activation [2].

It has been involved in the pathogenesis of many skin diseases, some of which are discussed below:

Osteopontin and infection

Osteopontin expression was elevated in cell-mediated diseases that affect the skin, especially in sarcoidosis and tuberculosis [3]. It regulates the immune system at many different levels. Within the immune system, OPN is secreted by activated T cells, NK cells, dendritic cells, and macrophages. It acts as a chemotactic molecule which promotes migration of inflammatory cells towards the wound site and also acts as an adhesive protein to keep cells at the site. OPN also functions as a pro-inflammatory cytokine where OPN can modulate the immune response by enhancing expression of T helper (Th1) cytokines and extracellular matrix-degrading enzymes [4].

Functional analysis in different models revealed that OPN enhanced Th1-mediated immunity by interacting with immune cells [5]. Osteopontin stimulates IL-12 secretion, and simultaneously down-regulates anti-inflammatory IL-10 secretion, OPN also has pro-migratory effects on immune cells where OPN is chemotactic for macrophages, dendritic cells (DC) and T cells [6].

Osteopontin deficiency was found to be associated with the dissemination of mycobacterial disease where the expression of OPN was correlated with an effective immune and inflammatory response. Osteopontin was contributed in resistance to mycobacterial infection in rodents as well as in humans. Osteopontin also contributed to protection against herpes simplex virus type 1, rotavirus, *L. monocytogenes* and *P. falciparum*. Many reports have suggested that OPN plays a role in the defense mechanisms against invading microorganisms, including bacteria, viruses and protozoa by inducing type 1 T helper cell–mediated immune responses (Th1) as well as granuloma formation through induction of interleukin-12 production by macrophages [6,7]. OPN exists in two isoforms, secreted (sOPN) and intracellular (iOPN) protein, sOPN affects the target cell functions by binding to their cell receptors; while iOPN binds to MyD88, the downstream protein of the Toll-like receptor. Also it has been reported that OPN binding to CD44v resulting in down-regulation of IL-10 production in macrophages, leading to inhibition of the Th2 immune response and binding to αvβ3 integrin receptor which led to the expression of IL-12, facilitating the Th1 response [8]. Shiratori *et al.* reported that quinolones succeeded to treat bacterial infections; in addition to their antibacterial effect; significantly enhance OPN secretion, due to the effect of most quinolones on the OPN gene promoter activity [8].

Osteopontin can be induced by viral antigens after ligation of toll-like receptors. Intracellular OPN enhances the production of IFN-α, resulting in a potent Th1 cell response, These complex regulatory functions of OPN are important in the pathology of microbial, allergic and autoimmune skin diseases [2,7].

Osteopontin and Systemic lupus erythematosus (SLE)

Serum OPN level was reported to be elevated in SLE patients compared with healthy donors [9]; Wong *et al.* [10] investigated the plasma concentration of OPN in 54 Chinese SLE patients with and without renal disease and demonstrated that OPN concentrations were significantly higher in both groups than in control group (p=0.001) which correlated positively with SLE disease activity index (r=0.308, p=0.023). They suggested that in combination with the inflammatory activities of IL-18, OPN can enhance Th1-mediated inflammatory

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process in the exacerbation of SLE and renal SLE.

In SLE patients with renal involvement, the concentration of OPN was positively correlated with pro-inflammatory cytokine IL- 18 level (r=0.404, p=0.037). This cytokine exerts a variety of effects on DCs, T lymphocytes and natural killer cells, and is an inducer of IFN-α to promote Th1 differentiation. Previous findings had highlighted the pathogenic role of Type I IFN in lupus nephritis. [11]. T lymphocytes activation can lead to production of autoantibodies and abnormalities in cytokine expression. When autoantibodies [against double-stranded DNA (ds-DNA), SS-B (anti-La), SS-A (anti-Ro), anti-RNP, anti-Sm] produced they can form complexes with antigens, which are deposited in organs, causing inflammation and tissue damage [12].

Osteopontin and psoriasis

Osteopontin has been involved in the onset of angiogenesis by a mechanism mediated by IL- 1 either by acting directly on endothelial cells and/or indirectly *via* mononuclear phagocyte engagement [13].

The local release of angiogenic growth factors is responsible for the uncontrolled endothelial cell proliferation that takes place during tumor neovascularization and in angiogenesis-dependent diseases such as diabetic retinopathy, psoriasis, and rheumatoid arthritis [14].

Chen *et al.* [15] reported that high plasma OPN levels are an unfavorable factor for development of cardiovascular disease in patients with psoriasis. Their results suggested that circulating OPN could be a marker for cardiovascular disease risk in psoriatic patients.

Buommino *et al.* [14] suggested a possible role for OPN as an early cytokine capable of driving Th1 cells responses in psoriatic patients. In particular, OPN was reported to be capable of interacting with integrins and CD44 to enhance Th1 and to inhibit Th2 cytokine gene expression.

Osteopontin and skin cancer:

Previous reports showed that deregulation of intracellular genes are important contributors to cancer development, recent reports indicate that alterations in the extracellular matrix microenvironment of cells with permanent genetic alterations can play a critical role in developing tumors [16].

OPN is one of the proteins that can affect the cells matrix microenvironment, because it is a highly inducible protein and has been shown to be expressed and secreted by tumor cells and cells in the stroma [17].

Scientists have shown in vivo that the lack of induced OPN expression in OPN-null mice significantly suppressed benign squamous papilloma development relative to wild-type mice when subjected to the two-stage (initiation-promotion) mouse skin chemical carcinogenesis model therefore directly supporting the role of OPN in facilitating tumourigenesis [18].

Chang *et al.* [16] showed that OPN was consistently expressed in all cases of cutaneous squamous cell carcinoma, which were capable of metastasis, but was not expressed in the solid basal cell carcinoma, which have no potential for metastasis, suggesting a potential role of OPN in facilitating metastasis.

In another study screened 14, 000 genes by microarray in metastatic melanoma nodules and normal nevi, reported 190 genes significantly overexpressed in metastasis. Fourteen genes of them showed more than 20-fold overexpression. Within this group, OPN was the most abundantly expressed gene. Moderate-to high OPN levels were detected in invasive and metastatic melanomas, whereas OPN levels were low in benign and dysplastic nevi and melanoma in situ [19].

In primary melanoma scientists found an association between increasing OPN staining and tumor thickness, higher mitotic index and invasive level. Higher OPN in tumors correlated with decreased recurrence-free and disease-specific survival. In addition, OPN was significantly associated with sentinel lymph node metastasis [20].

Osteopontin and allergic contact dermatitis (ACD)

The function of OPN was investigated during the sensitization phase of contact hypersensitivity (CHS). It was found that serum OPN guided Langerhans cells and myeloid dendritic cells (DC) into skin-draining lymph nodes, induced DC activation and polarized them toward a Th1-inducing phenotype [21].

It was also found that OPN secretion was important for the elicitation phase and the chronic phase of delayed-type allergic disease. Seier *et al.* found high levels of OPN secretion upon antigen-specific stimulation by memory T cells. In turn Th1 cell-derived interferon-γ (IFN-γ) specifically induced OPN in activated keratinocytes [22].

During the elicitation phase of ACD infiltrating CD45RO+ memory T cells secrete OPN. It was found that OPN gene expression in activated T cells was regulated by the transcription factor T-bet that controls CD4+ helper T cell commitment toward a Th1 phenotype. Furthermore, T-bet-dependent expression of OPN is essential for $CD4^+$ and $CD8^+$ effector cells to develop into Th1/Tc1 cells. When investigating whether OPN expression is a signal induced by antigen-specific activation of effector T cells, specifically stimulated $CD4^+$ or $CD8^+$ T cells from nickel-allergic donors with NiSO4 highly produced sOPN from both cell types [5,22]. During the elicitation phase of ACD OPN attracts additional antigen-specific T cells, monocytes, and DCs. OPN induces IL-12 secretion in macrophages and simultaneously inhibiting IL-10 production [23]. with subsequent induction of a Th1-skewing phenotype in myeloid-type DCs by inducing their IL-12 secretion, which further help to stabilizeTh1 response through antigen presentation by such polarized DCs [24].

Antigen-specific OPN expression was important for chronic phase of allergic contact dermatitis *in vivo*, because OPN-null mice have a reduced antigen-specific chronic response and established chronic inflammation was, in part, suppressed by anti-OPN antibodies. Also, in OPN null mice, less $CD4^+$ and $CD8^+$ effector T cells were found to invade the challenged skin [22]. These findings provide strong evidence that highly secreted sOPN from effector T cells is a major factor for establishment of chronic antigen-specific driven allergic inflammation.

In conclusion, Osteopontin is a multifunctional protein having a central role in pathogenesis of many skin diseases. Study the role of osteopontin in other skin diseases as lichen planus and ureamic pruritis is needed for better pathogenesis understanding. Osteopontin could be considered an interesting target for therapeutic intervention in inflammatory skin disease. More researches are needed to evaluate OPN as a prognostic serum marker in tumor as well as cardiovascular diseases especially in psoriasis patients.

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