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Chapter 4

Osteopontin (OPN) Gene Polymorphisms and Autoimmune Diseases

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http://dx.doi.org/10.5772/intechopen.69528

Abstract

Osteopontin (OPN) is a pleiotropic protein, important in bone remodeling and immune system signaling. OPN is synthesized in a variety of cells and tissues. It can be found not only in bone cells but also in immune cells (B and T lymphocytes, natural killer (NK) cells, natural killer T (NKT) cells, macrophages, neutrophils, and dendritic cells). OPN regulates T-helper 1/T-helper 2 (Th1/Th2) balance, stimulates B cells to antibodies production, regulates macrophages and neutrophils function, and activates dendritic cells. A number of factors, including hormones, cytokines, and polymorphisms of promoter region of OPN gene, regulate protein expression. OPN and variants of the OPN gene have been associated with the pathogenesis of multiple disorders, including systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, systemic sclerosis, inflammatory bowel diseases, asthma, type 1 diabetes, and many other. However, some studies gave different or inconclusive results. Thus, the role of OPN polymorphic variants in autoimmune diseases needs to be better defined and explored as a diagnostic and therapeutic target to monitor and treat immune-mediated conditions.

Keywords: asthma, autoimmune, gene, immunomodulation, inflammatory bowel diseases, multiple sclerosis, osteopontin, polymorphism, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, systemic sclerosis, type 1 diabetes

1. Introduction

There are more than 200 genetic loci that have been associated with one or more disorders. Today, at least 90 autoimmune diseases have been identified [1]. The etiology of autoimmune diseases is not fully elucidated; however, the causes are likely based on a combination of environmental and genetic factors, which lead to immunological abnormalities [2, 3]. Recent genome-wide association studies (GWAS) and single-nucleotide polymorphism (SNP) arrays...
have allowed the identification of several genetic variants associated with immune-mediated disorders. Genetic polymorphisms can influence the susceptibility, clinical manifestations, as well as response to therapy [4, 5].

A wide spectrum of inflammatory and immune mediators is currently under investigation in the context of autoimmune diseases. One of them is osteopontin (OPN), also known as early T lymphocyte activation-1 (Eta-1) or secreted phosphoprotein 1 (SPP-1). OPN is a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family proteins [6, 7]. OPN was identified in 1986 as a major sialoprotein of bone [8], where it is involved in many biological processes, such as biomineralization and remodeling [9]. OPN is synthesized in a variety of cells and tissues. It can be found in bone cells, immune cells (B and T lymphocytes, natural killer (NK) cells, natural killer T (NKT) cells, macrophages, neutrophils, dendritic cells), breast epithelial cells, neurons, Kupffer cells, hepatic macrophages, hepatic stellate cells (HSCs), lung cells, adipocytes, and many other [10]. OPN is a pleiotropic protein and its functions are linked to various physiological processes and pathological conditions. OPN, secreted by osteoblasts, osteoclasts, and osteocytes, is important in mineralization and bone resorption [9]. Recently, this protein was found to be relevant in regulation of immunity and inflammation, angiogenesis, oncogenesis, cancer progression, and apoptosis [10–12]. OPN interacts with most cells using two binding domains. Signaling via integrins (αvβ1, αvβ3, αvβ5, αvβ6, a8β1, a5β1, a9β1, a4β1, and α4β7) modulates the phosphorylation of kinases, which are involved in nuclear factor-kappa B (NF-κB) activation and regulation of cytokines production [13–16]. Moreover, OPN is an extracellular ligand for CD44 receptors. Signaling through CD44 modulates T cell chemotaxis, fibroblast adhesion, and interleukin (IL)-10 gene expression in macrophages [17]. OPN expression and function are influenced by post-translational modifications (phosphorylation, O-linked glycosylation, sialylation, tyrosine sulfation), hormones (calcitriol, retinoid acid, steroids), pro-inflammatory cytokines, growth and differentiation factors (epidermal growth factor, platelet-derived growth factor, transforming growth factor beta), and genetic polymorphisms of its promoter [18].

2. Osteopontin gene—structure and polymorphism

The human OPN gene (OPN) is mapped on the long arm of chromosome 4 (4q21-4q25). OPN contains seven exons (protein-coding regions) and six introns. The gene spans ~9 kb. The open reading frame (ORF) consists of 942 nucleotides from the start codon (in exon 2) to the stop codon (in exon 7) [19]. The 5′-untranslated (5′-UTR) region, of 67 bases, contains exon 1, which starts with transcription start site AGC (also referred to as the GCC box). The 3′-UTR region, of 415 bases, consists of the last part of exon 7 and includes three polyadenylation signals (AATAA). Exons 2–7 contain coding sequences: signal peptide and two first amino acids (exon 2), two Ser-Ser-Glu-Glu phosphorylation sequences (exons 3 and 5), two transglutaminase-reactive glutamine residues (exon 4), and aspartic acid-rich sequence (exon 6). Exon 7 encodes about half of the protein and contains the RGD motif and the central thrombin cleavage site [20].
OPN is highly polymorphic. Several polymorphisms in the human OPN gene have been identified. Single-nucleotide polymorphisms (SNPs) have been proposed as a tool for identifying genes associated with multiple autoimmune disorders. Polymorphisms in a human OPN have been reported to exhibit functional implications and have been evaluated in several conditions. Genetic association studies have suggested that some OPN SNPs may serve as a potential marker to predict immune-mediated diseases in some populations.

3. Osteopontin gene polymorphism and autoimmune diseases

3.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease. SLE is caused by environmental, hormonal, and genetic factors, which lead to immunological dysfunction [21, 22]. Deregulation of B and T lymphocytes activation leads to abnormalities in cytokine expression and production of autoantibodies, which form complexes with antigens. Complexes are deposited in organs and cause inflammation and tissue damage [23, 24]. Deregulation in cytokine expression is also a cause of tissue injury [25]. OPN promotes activation of T lymphocytes and regulates the T-helper 1/T-helper 2 (Th1/Th2) balance. OPN upregulates IL-12 production and downregulates IL-10 [26]. Recent findings revealed that OPN enhances interferon (IFN)-α expression through the interferon regulatory factor 7 (IRF7) activation upon toll-like receptor (TLR)9 stimulation in plasmacytoid dendritic cells (pDCs) [27] and stimulates antibodies production by B lymphocytes [26, 28]. In addition, it has been demonstrated that OPN enhances IL-17 producing Th17 cell responses [29, 30]. Thus, OPN plays an important role in regulating inflammation and immunity. Therefore, several studies have been performed to assess the association of OPN and predisposition to SLE.

In the literature, there are reports suggesting that OPN participates in the pathogenesis of SLE. It has been demonstrated that serum OPN level is elevated in SLE patients [31–36]. Moreover, OPN level correlates positively with disease activity index [33–35]. Polymorphic OPN alleles have been implicated in the mouse model of lupus [37]. The association between OPN gene polymorphisms and SLE susceptibility in humans has also been investigated.

In 2002, a study of Forton et al. [38] showed that polymorphic T allele of the polymorphism at position 707 in exon 7 (707C/T, rs1126616) is associated with opportunistic infections and renal insufficiency but is protective for avascular necrosis in Caucasian SLE patients. This was the first demonstration of a phenotypic association with an OPN polymorphism.

In a study of D’Alfonso et al. [39], a total of 13 SNPs in OPN gene were identified (six in the 5' flanking region, one in intron 3, three in exons 6, 7 and three in the 3'-UTR). Two polymorphisms: −156G/GG (rs7687316, in promoter) and +1239A/C (rs9138, in 3'-UTR) were significantly associated with SLE. The −156G and +1239C alleles were more frequent in SLE patients than in the control group. In addition, significant association was seen between lymphadenopathy and −156 genotypes. Significantly increased OPN serum level was detected in healthy individuals carrying +1239C.
In 2007, Xu et al. [40] demonstrated that SNP at position 9250 in exon 7 of the OPN gene (9250C/T) exists in the Chinese Han ethnic population and is associated with SLE. The frequency of TT genotype was lower and the frequency of TC genotype was higher in SLE patients than in controls. When authors separated patients and controls into women and men, significant differences of frequencies were noted in TT genotype, TC genotype and allele in women, but not in men. Moreover, the TT genotype was lower in SLE patients with lupus nephritis (LN) [41].

In a large study of SLE patients, Han et al. [42] reported that minor alleles of rs1126616 and rs9138 (T and C, respectively) were correlated with higher risk of SLE in European-American and African-American populations (in males, not in females). In addition, haplotype analysis identified rs1126616T-rs1126772A-rs9138C which demonstrated association with SLE in general, especially in males. It was the first description of a gender-specific human lupus genetic association.

In another study, Trivedi et al. [43] genotyped the rs11730582, rs28357094, rs6532040, and rs9138 SNPs in the OPN gene in SLE patients. The group proved that photosensitivity was associated with the risk allele rs9138C. In addition, the study demonstrated that the C allele of rs11730582 polymorphism is associated with thrombocytopenia and hemolytic anemia.

Kariuki et al. [44] revealed an association of the rs9138C allele with higher levels of OPN and INF-α in male SLE patients. Moreover, two SNPs, rs11730582 and rs28357094, were associated with the presence of anti-ribonucleoprotein (anti-RNP) autoantibodies.

Salimi and colleagues [36] genotyped the rs1126616 SNP in SLE patients and age, gender, and ethnically matched controls. There was no association between the polymorphism and SLE susceptibility. However, the frequency of CT and TT genotypes was higher in SLE patients with LN than in those without LN. In addition, no correlation between OPN serum levels and rs1126616 polymorphism has been found.

In conclusion, a number of studies demonstrated that some OPN polymorphic variants are associated with SLE susceptibility and/or clinical manifestations of the disease in humans. However, some studies gave different or inconclusive results. Reasons for such divergences may be low statistical power or clinical variety. Only few studies evaluated the correlation coefficient between OPN polymorphisms and SLE. Moreover, limited clinical data were provided.

3.2. Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system (CNS) with the basic pathological hallmark of inflammatory demyelination in the white matter and cortex, implying a disturbance of the symbiotic relationship of the axon and myelin sheath [45]. Infiltrating CD4+ Th1 cells, which produce IFN-γ, and CD4+ Th17, which produce IL-17, has been shown to be involved in pathogenesis of MS. In addition, activated monocytes and B cells are present in the CNS, which results in degradation of the myelin sheath surrounding nerves [45, 46]. For MS development, both genetic predisposition and environmental factors are responsible [47]. OPN, a pleiotropic cytokine, plays an important role in immune-mediated
disorders. OPN may influence development of MS through enhancing the pro-inflammatory Th1 and Th17 cell responses and inhibiting the anti-inflammatory Th2 cell responses [11, 29].

In the literature, there are reports suggesting that OPN participates in the pathogenesis of MS. OPN was identified as one of the disease-specific markers in plaques from brains of patients with MS [48]. In addition, it has been demonstrated that this protein is expressed higher in blood and CNS in MS patients than in healthy controls [49]. Moreover, OPN level correlated positively with disease activity and relapse rate [50–53]. However, there are studies which showed that higher OPN serum level in MS patients is not associated with disease severity [54, 55].

A large body of data indicates that OPN gene variants have an impact on MS pathogenesis and progression.

In a study of Niino et al. [56], three SNPs in the OPN gene (8090 in a coding region of exon 6, 9250 in a coding region of exon 7, and 9583 in the 3′-UTR region of exon 7) were analyzed in Japanese MS patients and healthy controls. It has been demonstrated that the CC genotype at the 8090th position was more prevalent in MS than in the control group. For the 9583rd position polymorphism, patients with GG genotype showed a later disease onset than GA and AA genotypes. However, there were no significant correlations between OPN variants and disease progression. These results suggest that the 8090th polymorphism might be associated with susceptibility to MS, whereas the 9583rd polymorphism with age of onset of MS.

In another study, Caillier and colleagues [57] investigated whether four SNPs (327T/C, 795C/T, 1128A/G, and 1284A/C) in the OPN gene were correlated with susceptibility to MS or clinical manifestations in a group of MS patients. As a result of the strong disequilibrium observed between SNPs within the OPN locus, only two SNPs were selected to study potential genotype-phenotype correlations: 1284A/C and 327T/C. No evidence of genetic association between the OPN polymorphisms and MS susceptibility has been observed. However, a modest trend for association with disease course was detected in patients carrying at least one wild-type 1284A allele. Patients with this allele/genotype were less likely to have a mild disease course and were at increased risk for a secondary progressive clinical type.

Similar to study of Caillier et al., no evidence of association between OPN variants and MS susceptibility and severity was observed in a study of Hensiek et al. [58].

Chiocchetti et al. [59, 60] identified four SNPs in the OPN gene: +282T/C (rs4754), +750C/T (rs11226616), +1083A/G (rs1126772), and +1239A/C (rs9138) in 3′ UTR, which form three haplotypes: A (282T-750C-1083A-1239A), B (282C-750T-1083A-1239C), and C (282C-750T-1083G-1239C). The group demonstrated that haplotype A homozygotes showed lower risk of developing MS and lower OPN serum levels than haplotype B or C carriers. In the next study, analysis was extended to a gene polymorphism at the 5′ end on the −156G/GG SNP and replicated previous findings at the 3′ end on the +1239A/C SNP. It has been demonstrated that +1239A/C SNP was associated with MS development. +1239A and −156/GG homozygosity was associated with slower disease progression. Moreover, patients homozygous for +1239A showed lower relapse rate than those carrying +1239C [61].
Most of the results indicate that OPN and its gene SNPs might be a good marker for the susceptibility to and severity of MS. Despite this, further studies are needed to improve our understanding of the OPN gene role in disease pathogenesis.

### 3.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects joints, connective tissues, muscle, tendons, and fibrous tissue [62]. In RA, immune cells (monocytes, macrophages, B cells, CD4+ and CD8+ T cells, neutrophils) infiltrate the synovial fluid. Activation of T cells leads to the production of pro-inflammatory cytokines. Humoral adaptive immunity is also integral to RA. B cells are activated through interactions with T cells and through soluble cytokines that enhance their proliferation and differentiation. Mature B cells (plasma cells) are a source of autoantibodies (known as rheumatoid factors and anti-citrullinated peptide antibodies, ACPA). Synovial macrophages produce pro-inflammatory cytokines, including tumor necrosis factor (TNF), IL-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GMCSF). Neutrophils in the synovial fluid are in an activated state, releasing oxygen-derived free radicals that promote joints damage [63]. Gene-environment interactions appear as the most plausible underlying cause of RA.

A wide spectrum of immune mediators is currently under investigation in the context of RA pathogenesis and progression. One of them is OPN. This protein has been found to be elevated in plasma and synovial fluid of RA patients as well as in peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells [64–66]. High OPN level has been correlated with serum C-reactive protein (CRP) level and inflammation markers [67]. It has been demonstrated that OPN concentration is higher during disease progression. Moreover, OPN correlates with bone resorption markers [68]. To support the role of OPN in RA, several studies have been conducted to investigate the role of OPN gene variants in disease pathogenesis and progression.

In 2005, Urcelay et al. [69] studied the association of four OPN SNPs (327T/C in the coding region of exon 6, 795C/T in the coding region of exon 7, 1128A/G, and 1284A/C in the 3′-UTR) and predisposition to RA in a Spanish population. Analysis of the haplotypes defined by these SNPs did not identify association with RA.

In another study, Xu and colleagues [66] investigated whether genetic polymorphisms of the OPN gene were associated with susceptibility to RA in Chinese Han nationality. Analysis revealed a total of 14 SNPs. Finally, six SNPs were selected for analysis (two newly identified SNPs in the promoter region: −631G/T and −458T/C and four in exons: rs4754, rs1126616, rs1126772, rs9138). Similarly to a study of Urcelay et al., prevalence of OPN genotype and allele frequencies did not differ significantly between RA patients and healthy controls.

For the first time, the association between OPN gene polymorphism and RA susceptibility was demonstrated in a study of Ceccarelli et al. [70] in an Italian cohort. A statistically significant association between RA and OPN −156G/GG (rs7687316) was found. There was no association of +1239A/C (rs9138) polymorphism and RA.

In 2013, Gazal et al. [71] evaluated the contribution of the OPN rs11439060 (−156/-) and rs9138 (1239A/C) SNPs in a large cohort of RA patients and controls. The group reported a
significant contribution of the combination of the rs11439060 and rs9138 frequent alleles to risk of RA, especially in ACPA-negative patients. In the next study of this group, it has been demonstrated that rs9138 variants contribute to joint damage progression in ACPA-negative patients [72].

OPN is relatively a newly identified RA susceptibility gene. Data about the role of OPN variants in disease pathogenesis are very scanty and contradictory. Therefore, more studies are necessary for further elucidation of OPN polymorphism role in RA.

3.4. Systemic sclerosis

Systemic sclerosis (SSc) is an immune-mediated connective tissue disorder, characterized by an overproduction of collagen, immune dysfunction, and blood vessel damage [73]. Multiple organ damage is a consequence of this disease [74]. Immunological abnormalities of innate and adaptive immune system, including mononuclear cell infiltration of affected tissues, deregulation of cytokines (transforming growth factor beta [TGFβ], TNFα, IL-6, IL-10, IL-17, IL-4, IL-13) and chemokines (CCL18, CCL19, CXCL13, CCL2, CCL3, CXCL4, CCR1, CCR2, CCR3) synthesis, and autoantibodies production, have long been recognized in SSc [75].

Despite intense research, the pathogenesis of SSc is only partly understood, but it likely involves an interaction between environmental factors in a genetic predisposing background [76].

OPN, plays an important role during both acute and chronic inflammation. In the literature, there are reports suggesting that this protein participates in the pathogenesis of SSc. OPN has a chemotactic and pro-fibrotic properties [77, 78]. Moreover, enhances the pro-inflammatory Th1 cell response, which is believed to be crucial in SSc pathogenesis. It has been demonstrated that mice with OPN overexpression have higher levels of anti-DNA autoantibodies, as well as increased gamma globulins [26]. This protein has been found to be elevated in plasma in SSc patients [79–81]. In addition, high OPN level was found to be correlated with serum CRP level [79].

The association between OPN gene polymorphisms and SSc susceptibility in humans has been investigated in a study of Barizzone et al. [82]. The group analyzed the association of two OPN SNPs: −156G/GG and +1239A/C and serum level of OPN in Italian SSc patients and controls. In SSc patients, there was a significantly increased frequency of the alleles −156G and +1239C, compared with controls. Moreover, OPN serum levels were significantly higher in SSc patients. However, no association between OPN levels and +1239 or −156 genotypes was observed.

These few data suggest that OPN genetic variations may have a role in SSc susceptibility, but further studies are needed to confirm these findings.

3.5. Inflammatory bowel diseases

Inflammatory bowel diseases (IBDs), especially Crohn’s disease (CD) and ulcerative colitis (UC), are idiopathic, multifactorial disorders, characterized by chronic intestinal inflammation [83]. CD is a transmural and segmental inflammatory disease. It may affect any part of the gastrointestinal tract, from the mouth to the anus, but is located usually in the terminal ileum.
It is characterized by the formation of ulcers, fistulas, stenosis, and intestinal granulomas, with periods of aggravation and remission. UC can affect only the mucosa of the colon and the rectum [84]. The etiology of IBDs is not fully elucidated. However, available evidence suggests that an abnormal immune response against the microorganisms of the intestinal flora is responsible for the disease in genetically susceptible individuals [85]. CD is characterized as a Th1 directed disease, with elevated CD4+ T-cell synthesis of IFN-γ and high TNF-α and IL-12 production by activated macrophages. UC is associated with incorrect Th2 response mediated by NKT cells, which secrete IL-13 [86].

In the literature, there are reports suggesting that OPN, as an immunomodulator, participates in the pathogenesis of IBDs in animal models and in humans. It has been demonstrated that serum OPN level is elevated in IBD patients and correlates with disease activity [87–91]. However, some studies in humans and in animal models of colitis gave opposite results, suggesting a dual or protective function of OPN in intestinal inflammation [86, 91–99].

The association between OPN gene polymorphisms and IBD susceptibility in humans has also been investigated. In a study of Glas et al. [100], 9 OPN SNPs (rs2728127, rs2853744, rs1730582, rs11739060, rs28357094, rs4754=p.Asp80Asp, rs1126616=p.Ala236Ala, rs1126772, and rs9138) were analyzed in a large group of Caucasian individuals (841 patients with CD, 473 patients with UC, and 1505 healthy unrelated controls). For rs4754, rs1126616, rs1126772, and rs9138, significantly different distributions between male and female CD patients were observed (rs4754 was protective in male patients). None of the other investigated OPN SNPs was associated with CD or UC susceptibility. However, several haplotypes demonstrated significant associations with CD susceptibility. The strongest association was found for a haplotype rs2728127-rs2853744-rs11730582-rs11439060-rs28357094-rs112661-rs1126772-rs9138. Moreover, no correlation was found between SNPs and IL-22 serum levels. The results argue against a major role for OPN gene polymorphism in the IBDs susceptibility. However, further analysis is required to clarify the role of OPN variants in the pathogenesis of the disease.

3.6. Type 1 diabetes

Type 1 diabetes (T1D) is a chronic, immune-mediated metabolic disorder of childhood and adolescence. T1D develops as a result of an autoimmune process, leading to β-cell destruction [101]. Activated NK cells, DCs, macrophages, and T-cells are attracted to the islets, which is followed by production of pro-inflammatory cytokines and free radicals, causing β-cell dysfunction and apoptosis [101, 102].

OPN plays an essential role in the regulation of immune cell response. It has been demonstrated that OPN induces adipose tissue inflammation, upregulates pro-inflammatory cytokines, and stimulates B lymphocytes to antibodies production. Consequently, OPN promotes the destruction of pancreatic β-cell and development of T1D [10, 103]. Therefore, several studies have been performed to assess the association of OPN and predisposition to T1D. This protein has been found to be elevated in pediatric and adult patients with T1D [104–106]. Moreover, OPN has correlated with some clinical and biochemical parameters in T1D patients, including higher body mass index (BMI), systolic blood pressure (SBP), diastolic
blood pressure (DBP), lower high-density lipoprotein (HDL), and microalbuminuria [104, 107]. In addition, OPN has been found to be an independent predictor of diabetic retinopathy and nephropathy [107].

The OPN encoding gene can be considered as a candidate for genetic susceptibility to T1D. Several studies have been conducted to investigate the role of OPN polymorphisms in disease pathogenesis. In 2009, Marciano et al. [108] genotyped T1D patients and controls for three OPN SNPs: −156G/GG, −66T/G (in promoter) and biallelic ins/del variant TG/TGTG at +245 in the first intron. It has been demonstrated that the G allele at −66 SNP had higher frequency in controls than in patients. The association has been confirmed in females but not in males.

In another study, Chiocchietti and colleagues [109] evaluated the role of +1239A/C SNP in a 3′-UTR of OPN gene in an Italian T1D patients and controls. The analysis revealed that C allele carriers displayed higher risk of T1D than A allele carriers. The group suggested that this SNP is associated with T1D development.

In 2013, a study of Karamizadeh et al. [105] showed that rs1126772 SNP is not associated with T1D children, although serum OPN levels were significantly higher in diabetic patients than in controls.

The results from these studies are inconclusive; thus, more research is necessary for further elucidation of OPN polymorphism role in T1D.

3.7. Asthma

Asthma is the most common chronic lung disease. It is characterized by airway inflammation and respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough [110]. Multiple immune cells are involved in the inflammatory response in asthma. Th2 cells, which produce IL-4, IL-5, and IL-13, are responsible for eosinophils accumulation in the lungs of asthmatic patients. Th17 cells release IL-17 and recruit neutrophils, which attract eosinophils indirectly. Th1 and regulatory T (Treg) lymphocytes are also involved in the development of asthma. An elevation of Th17 cells, the absence of Treg cells, and an imbalance in Treg/Th17 are associated with the disease [110–112].

Asthma is thought to be caused by a combination of genetic and environmental factors. A wide spectrum of immune mediators is currently under investigation in the context of this disorder. OPN plays an important role during inflammation and regulates function of immune cells. In the literature, there are reports suggesting that this protein participates in the pathogenesis of asthma. Several studies have demonstrated that OPN level is increased in asthmatic patients and is associated with disease phenotypes [113–116]. In addition, the chromosomal region of 4q24 (where OPN gene is mapped) has been associated with atopy in asthmatic patients [117]. These studies suggest that OPN gene may be a candidate gene for asthma susceptibility.

The case-control study of Tanino et al. [118] investigated the association of OPN variants with serum immunoglobulin E (IgE) levels, atopy, and asthma in a Japanese population. The group genotyped three promoters and two exon polymorphisms at OPN gene: −1687A/G; −381T/C;
−94 deletion/G; 5891C/T; and 7052T/C. Association analyses demonstrated that homozygotes for the 5891T allele and 7052C allele were significantly associated with increased levels of total IgE in non-asthmatic subjects. However, these variants were not associated with asthma and atopy.

Different results have been obtained in a study of Arjomandi and colleagues [119]. To determine whether SNPs in OPN gene are associated with risk of asthma, six SNPs (rs6812524, rs7435825, rs1126616, rs4660, rs1126772, and rs9138) have been genotyped in the Latino Americans population of 294 Mexican and 365 Puerto Rican parent-child asthma trios. Haplotype analysis identified rs1126616C-rs1126772A-rs9138A to be associated with an increased risk and severity of asthma in Puerto Rican subjects with elevated IgE. However, there was no association between the SNPs and asthma outcomes in Mexicans.

Only these two studies have been conducted to investigate the role of OPN gene variants in asthma pathogenesis and progression; therefore, further investigation in this field is indispensable.

### 3.8. Sarcoidosis

Sarcoidosis is a chronic inflammatory condition characterized by the formation of non-caseating epithelioid granulomata at various sites in the body (lungs, thorax, skin, eyes, liver, heart, and nervous and musculoskeletal system) [120]. The cause of the disease is still unknown, but several immune aberrations are thought to play a role in its pathogenesis. Studies have revealed an increase of B-cell activity with elevated plasma levels of immunoglobulins and immune-complexes in patients. In addition, inflammation in sarcoidosis is dependent on persistent stimulation by CD4+ T h1 cells [120, 121]. Sarcoidosis is thought to be caused by a combination of genetic and environmental factors, but the exact etiology remains unclear. In the literature, there are reports suggesting that OPN participates in the pathogenesis of sarcoidosis. High levels of this protein have been found to be increased in serum and granulomas from patients with sarcoidosis [122–124]. Moreover, it has been demonstrated that OPN induced the chemotaxis of T cells and acted as an adhesion factor for activated T cells [123].

The OPN encoding gene can be considered as a candidate for susceptibility to sarcoidosis. Two studies have been conducted to investigate the role of OPN polymorphisms in disease pathogenesis. In 2004, Akahoshi et al. [125] investigated the 2514C/T SNP in Japanese patients with sarcoidosis and in healthy controls. The group did not find any significant association between genotypes/alleles and disease pathogenesis.

In another study, Maver and colleagues [126] genotyped three OPN SNPs: rs11730582, rs11728697, and rs4754 in Slovenian patients and healthy subjects. The analysis revealed a significant difference in genotype frequencies at rs4754 SNP in patients and controls. However, these results failed to reach significance after correction for multiple testing. In addition, analysis demonstrated that frequency of rs11730582T-rs11728697T-rs4754T haplotype was decreased in the group of patients compared to controls. It has been suggested that TTT haplotype of OPN gene is a protective factor in sarcoidosis.
These scanty studies have yielded conflicting and inconclusive results. Thus, further analyses are required to understand the role of OPN and its gene polymorphism in sarcoidosis.

4. Conclusions and future perspectives

OPN is highly expressed by various cell types, including cells of the immune system. This pleiotropic protein regulates both, innate and adaptive immune response. A large number of publications suggest that OPN participates in the pathogenesis of multiple autoimmune conditions. Moreover, there are reports suggesting the role of OPN gene polymorphism in the pathogenesis and/or clinical manifestations of immune-mediated diseases. However, some investigations failed to demonstrate any associations of OPN SNPs with autoimmune conditions. The main causes for these differences include ethnic, environmental and still unknown factors. Moreover, some studies do not meet the current rigorous standards for non-biased large-cohort trials. Future research should focus on selecting the best study groups to investigate the role of OPN variants in diseases pathogenesis and progression. Studies of OPN polymorphisms must take into account the gene-environment, gene-gene interactions, and ethnic factors.

The role of OPN polymorphic variants in autoimmune diseases needs to be better defined and explored as a diagnostic and therapeutic target to monitor and treat immune-mediated conditions. Advances in understanding specific SNPs in OPN may be helpful to create genetic profiles for predisposition to autoimmune diseases in order to adopt prevention strategies from childhood to adulthood.

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Genetic Polymorphisms


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