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# Osteopontin (OPN) Gene Polymorphisms and Autoimmune Diseases

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## 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

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## 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 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 ( $\alpha v\beta 1$ ,  $\alpha v\beta 3$ ,  $\alpha v\beta 5$ ,  $\alpha v\beta 6$ ,  $\alpha 8\beta 1$ ,  $\alpha 5\beta 1$ ,  $\alpha 9\beta 1$ ,  $\alpha 4\beta 1$ , and  $\alpha 4\beta 7$ ) modulates the phosphorylation of kinases, which are involved in nuclear factor-kappa B (NF- $\kappa$ B) 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)- $\alpha$  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 -156G 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- $\alpha$  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<sup>+</sup> Th1 cells, which produce IFN- $\gamma$ , and CD4<sup>+</sup> 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<sup>+</sup> and CD8<sup>+</sup> 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 (GM-CSF). 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-/G) 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 [TGF $\beta$ ], TNF $\alpha$ , 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<sup>+</sup> T-cell synthesis of IFN- $\gamma$  and high TNF- $\alpha$  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, rs11730582, 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-rs1126616-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  $\beta$ -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  $\beta$ -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  $\beta$ -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<sup>+</sup> Th1 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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#### References

- [1] Ercolini A, Miller SD. The role of infections in autoimmune disease. *Clinical and Experimental Immunology*. 2009;**155**:1-15. DOI: 10.1111/j.1365-2249.2008.03834.x
- [2] Campbell AW. Autoimmunity and the gut. *Autoimmune Diseases*. 2014;**2014**:152428. DOI: 10.1155/2014/152428

- [3] Davidson A, Diamond B. Autoimmune diseases. *The New England Journal of Medicine*. 2001;**345**:340-350. DOI: 10.1056/NEJM200108023450506
- [4] Costenbader KH, Gay S, Alarcón-Riquelme ME, Iaccarino L, Doria A. Genes, epigenetic regulation and environmental factors: Which is the most relevant in developing autoimmune diseases? *Autoimmunity Reviews*. 2012;**11**:604-609. DOI: 10.1016/j.autrev.2011.10.022
- [5] Cho JH, Feldman M. Heterogeneity of autoimmune diseases: Pathophysiologic insights from genetics and implications for new therapies. *Nature Medicine*. 2015;**21**:730-738. DOI: 10.1038/nm.3897
- [6] Fisher LW, Torchia DA, Fohr B, Young MF, Fedarko NS. Flexible structures of SIBLING proteins, bone sialoprotein, and osteopontin. *Biochemical and Biophysical Research Communications*. 2001;**280**:460-465. DOI: 10.1006/bbrc.2000.4146
- [7] Ramaiah SK, Rittling S. Pathophysiological role of osteopontin in hepatic inflammation, toxicity, and cancer. *Toxicological Sciences*. 2008;**103**:4-13. DOI: 10.1093/toxsci/kfm246
- [8] Oldberg A, Franzén A, Heinegård D. Cloning and sequence analysis of rat bone sialoprotein (osteopontin) cDNA reveals an Arg-Gly-Asp cell-binding sequence. *Proceedings of the National Academy of Sciences of the United States of America*. 1986;**83**:8819-8823
- [9] Kruger TE, Miller AH, Godwin AK, Wang J. Bone sialoprotein and osteopontin in bone metastasis of osteotropic cancers. *Critical Reviews in Oncology/Hematology*. 2014;**89**:330-341. DOI: 10.1016/j.critrevonc.2013.08.013
- [10] Denhardt DT, Guo X. Osteopontin: A protein with diverse functions. *FASEB Journal*. 1993;**7**:1475-1482
- [11] Cantor H. The role of Eta-1/osteopontin in the pathogenesis of immunological disorders. *Annals of the New York Academy of Sciences*. 1995;**760**:143-150
- [12] Cao DX, Li ZJ, Jiang XO, Lum YL, Khin E, Lee NP, Wu GH, Luk JM. Osteopontin as potential biomarker and therapeutic target in gastric and liver cancers. *World Journal of Gastroenterology*. 2012;**18**:3923-3930. DOI: 10.3748/wjg.v18.i30.3923
- [13] Hu DD, Lin EC, Kovach NL, Hoyer JR, Smith JW. A biochemical characterization of the binding of osteopontin to integrins alpha v beta 1 and alpha v beta 5. *The Journal of Biological Chemistry*. 1995;**270**:26232-26238
- [14] Green PM, Ludbrook SB, Miller DD, Horgan CM, Barry ST. Structural elements of the osteopontin SVVYGLR motif important for the interaction with alpha(4) integrins. *FEBS Letters*. 2001;**503**:75-79
- [15] Yokosaki Y, Tanaka K, Higashikawa F, Yamashita K, Eboshida A. Distinct structural requirements for binding of the integrins alphavbeta6, alphavbeta3, alphavbeta5, alpha5beta1 and alpha9beta1 to osteopontin. *Matrix Biology: Journal of the International Society for Matrix Biology*. 2005;**24**:418-427. DOI: 10.1016/j.matbio.2005.05.005

- [16] Urtasun R, Lopategi A, George J, Leung TM, Lu Y, Wang X, Ge X, Fiel MI, Nieto N. Osteopontin, an oxidant stress sensitive cytokine, up-regulates collagen-I via integrin  $\alpha(V)\beta(3)$  engagement and PI3K/pAkt/NF $\kappa$ B signaling. *Hepatology*. 2012;**55**:594-608. DOI: 10.1002/hep.24701
- [17] Weber GF, Ashkar S, Glimcher MJ, Cantor H. Receptor-ligand interaction between CD44 and osteopontin (Eta-1). *Science*. 1996;**271**:509-512
- [18] Subraman V, Thiyagarajan M, Malathi N, Rajan ST. OPN -Revisited. *Journal of Clinical and Diagnostic Research*. 2015;**6**:ZE10-ZE13. DOI: 10.7860/JCDR/2015/12872.6111
- [19] Hijiya N, Setoguchi M, Matsuura K, Higuchi Y, Akizuki S, Yamamoto S. Cloning and characterization of the human osteopontin gene and its promoter. *The Biochemical Journal*. 1994;**303**:255-262
- [20] Rodrigues LR, Teixeira JA, Schmitt FL, Paulsson M, Lindmark-Månsson H. The role of osteopontin in tumor progression and metastasis in breast cancer. *Cancer Epidemiology, Biomarkers and Prevention*. 2007;**16**:1087-1097. DOI: 10.1158/1055-9965.EPI-06-1008
- [21] Kotzin BL. Systemic lupus erythematosus. *Cell*. 1996;**85**:303-306
- [22] Mills JA. Systemic lupus erythematosus. *The New England Journal of Medicine*. 1994;**330**:1871-1879
- [23] Giles BM, Boackle SA. Linking complement and anti-dsDNA antibodies in the pathogenesis of systemic lupus erythematosus. *Immunology Research*. 2013;**55**:10-21. DOI: 10.1007/s12026-012-8345-z
- [24] Marks SD, Tullus K. Autoantibodies in systemic lupus erythematosus. *Pediatric Nephrology*. 2012;**27**:1855-1868. DOI: 10.1007/s00467-011-2078-4
- [25] Yap DY, Lai KN. The role of cytokines in the pathogenesis of systemic lupus erythematosus - From bench to bedside. *Nephrology*. 2013;**18**:243-255. DOI: 10.1111/nep.12047
- [26] Ashkar S, Weber GF, Panoutsakopoulou V, Sanchirico ME, Jansson M, Zawaideh S, Rittling SR, Denhardt DT, Glimcher MJ, Cantor H. Eta-1 (osteopontin): An early component of type-1 (cell-mediated) immunity. *Science*. 2000;**287**:860-864
- [27] Shinohara ML, Lu L, Bu J, Werneck MB, Kobayashi KS, Glimcher LH, Cantor H. Osteopontin expression is essential for interferon-alpha production by plasmacytoid dendritic cells. *Nature Immunology*. 2006;**7**:498-506. DOI: 10.1038/ni1327
- [28] Lampe MA, Patarca R, Iregui MV, Cantor H. Polyclonal B cell activation by the Eta-1 cytokine and the development of systemic autoimmune disease. *Journal of Immunology*. 1991;**147**:2902-2906
- [29] Murugaiyan G, Mittal A, Weiner HL. Increased osteopontin expression in dendritic cells amplifies IL-17 production by CD4<sup>+</sup> T cells in experimental autoimmune encephalomyelitis and in multiple sclerosis. *Journal of Immunology*. 2008;**181**:7480-7488

- [30] Shinohara ML, Kim JH, Garcia VA, Cantor H. Engagement of the type I interferon receptor on dendritic cells inhibits T helper 17 cell development: Role of intracellular osteopontin. *Immunity*. 2008;**29**:68-78. DOI: 10.1016/j.immuni.2008.05.008
- [31] Katagiri Y, Mori K, Hara T, Tanaka K, Murakami M, Uede T. Functional analysis of the osteopontin molecule. *Annals of the New York Academy of Sciences*. 1995;**760**:371-374
- [32] Lou B, Lv J, Zheng M. The relationship between osteopontin plasma concentration and disease activity in systemic lupus erythematosus. *Chinese Journal of Dermatology*. 2006;**39**:320-321
- [33] Wong CK, Lit LC, Tam LS, Li EK, Lam CW. Elevation of plasma osteopontin concentration is correlated with disease activity in patients with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2005;**44**:602-606. DOI: 10.1093/rheumatology/keh558
- [34] Rullo OJ, Woo JM, Parsa MF, Hoftman AD, Maranian P, Elashoff DA, Niewold TB, Grossman JM, Hahn BH, McMahan M, McCurdy DK, Tsao BP. Plasma levels of osteopontin identify patients at risk for organ damage in systemic lupus erythematosus. *Arthritis Research & Therapy*. 2013;**15**:R18. DOI: 10.1186/ar4150
- [35] Afify MF, Mohamed GB, El-Maboud MA, Abdel-Latif EA. Plasma concentration of osteopontin (OPN) in children with systemic lupus erythematosus: Relationship with disease activity. *The Open Autoimmunity Journal*. 2009;**1**:59-63. DOI: 10.2174/1876894600901010059
- [36] Salimi S, Noora M, Nabizadeh S, Rezaei M, Shahraki H, Milad MK, Naghavi A, Farajian-Mashhadi F, Zakeri Z, Sandoughi M. Association of the osteopontin rs1126616 polymorphism and a higher serum osteopontin level with lupus nephritis. *Biomedical Reports*. 2016;**4**:355-360. DOI: 10.3892/br.2016.589
- [37] Miyazaki T, Ono M, Qu WM, Zhang MC, Mori S, Nakatsuru S, Nakamura Y, Sawasaki T, Endo Y, Nose M. Implication of allelic polymorphism of osteopontin in the development of lupus nephritis in MRL/lpr mice. *European Journal of Immunology*. 2005;**35**:1510-1520. DOI: 10.1002/eji.200425672
- [38] Forton AC, Petri MA, Goldman D, Sullivan KE. An osteopontin (SPP1) polymorphism is associated with systemic lupus erythematosus. *Human Mutation*. 2002;**19**:459. DOI: 10.1002/humu.9025
- [39] D'Alfonso S, Barizzone N, Giordano M, Chiocchetti A, Magnani C, Castelli L, Indelicato M, Giacomelli F, Marchini M, Scorza R, Danieli MG, Cappelli M, Migliaresi S, Bigliardo B, Sabbadini MG, Baldissera E, Galeazzi M, Sebastiani GD, Minisola G, Ravazzolo R, Dianzani U, Momigliano-Richiardi P. Two single-nucleotide polymorphisms in the 5' and 3' ends of the osteopontin gene contribute to susceptibility to systemic lupus erythematosus. *Arthritis and Rheumatism*. 2005;**52**:539-547. DOI: 10.1002/art.20808
- [40] Xu AP, Bai J, Lü J, Liang YY, Li JG, Lai DY, Wan X, Huang HH. Osteopontin gene polymorphism in association with systemic lupus erythematosus in Chinese patients. *Chinese Medical Journal*. 2007a;**120**:2124-2128

- [41] Xu AP, Liang YY, Lü J, Li JG, Wang Z. Association of osteopontin gene polymorphism with lupus nephritis in Chinese Han population. *Journal of Southern Medical University*. 2007b;**27**:1348-1351. Chinese
- [42] Han S, Guthridge JM, Harley IT, Sestak AL, Kim-Howard X, Kaufman KM, Namjou B, Deshmukh H, Bruner G, Espinoza LR, Gilkeson GS, Harley JB, James JA, Nath SK. Osteopontin and systemic lupus erythematosus association: A probable gene-gender interaction. *PLoS One*. 2008;**3**:e0001757. DOI: 10.1371/journal.pone.0001757
- [43] Trivedi T, Franek BS, Green SL, Kariuki SN, Kumabe M, Mikolaitis RA, Jolly M, Utset TO, Niewold TB. Osteopontin alleles are associated with clinical characteristics in systemic lupus erythematosus. *Journal of Biomedicine and Biotechnology*. 2011;**2011**:802581. DOI: 10.1155/2011/802581
- [44] Kariuki SN, Moore JG, Kirou KA, Crow MK, Utset TO, Niewold TB. Age- and gender-specific modulation of serum osteopontin and interferon-alpha by osteopontin genotype in systemic lupus erythematosus. *Genes and Immunity*. 2009;**10**:487-494. DOI: 10.1038/gene.2009.15
- [45] Trapp BD, Nave KA. Multiple sclerosis: An immune or neurodegenerative disorder? *Annual Review of Neuroscience*. 2008;**31**:247-269. DOI: 10.1146/annurev.neuro.30.051606.094313
- [46] Trager N, Butler JT, Haque A, Ray SK, Beeson C, Banik NL. The involvement of calpain in CD4+ T helper cell bias in multiple sclerosis. *Journal of Clinical and Cellular Immunology*. 2013;**4**:1000153. DOI: 10.4172/2155-9899.1000153
- [47] Nylander A, Hafler DA. Multiple sclerosis. *The Journal of Clinical Investigation*. 2012;**122**:1180-1188. DOI: 10.1172/JCI58649
- [48] Chabas D, Baranzini SE, Mitchell D, Bernard CC, Rittling SR, Denhardt DT, Sobel RA, Lock C, Karpuz M, Pedotti R, Heller R, Oksenberg JR, Steinman L. The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease. *Science*. 2001;**294**:1731-1735. DOI: 10.1126/science.1062960
- [49] Sinclair C, Mirakhur M, Kirk J, Farrell M, McQuaid S. Up-regulation of osteopontin and alphaBeta-crystallin in the normal-appearing white matter of multiple sclerosis: An immunohistochemical study utilizing tissue microarrays. *Neuropathology and Applied Neurobiology*. 2005;**31**:292-303. DOI: 10.1111/j.1365-2990.2004.00638.x
- [50] Comabella M, Pericot I, Goertsches R, Nos C, Castillo M, Blas Navarro J, Río J, Montalban X. Plasma osteopontin levels in multiple sclerosis. *Journal of Neuroimmunology*. 2005;**158**:231-239. DOI: 10.1016/j.jneuroim.2004.09.004
- [51] Szalardy L, Zadori D, Simu M, Bencsik K, Vecsei L, Klivenyi P. Evaluating biomarkers of neuronal degeneration and neuroinflammation in CSF of patients with multiple sclerosis-osteopontin as a potential marker of clinical severity. *Journal of Neurological Science*. 2013;**331**:38-42. DOI: 10.1016/j.jns.2013.04.024
- [52] Vogt MH, Floris S, Killestein J, Knol DL, Smits M, Barkhof F, Polman CH, Nagelkerken L. Osteopontin levels and increased disease activity in relapsing-remitting multiple

- sclerosis patients. *Journal of Neuroimmunology*. 2004;**155**:155-160. DOI: 10.1016/j.jneuroim.2004.06.007
- [53] Wen SR, Liu GJ, Feng RN, Gong FC, Zhong H, Duan SR, Bi S. Increased levels of IL-23 and osteopontin in serum and cerebrospinal fluid of multiple sclerosis patients. *Journal of Neuroimmunology*. 2012;**244**:94-96. DOI: 10.1016/j.jneuroim.2011.12.004
- [54] Kivisäkk P, Healy BC, Francois K, Gandhi R, Gholipour T, Egorova S, Sevdalinova V, Quintana F, Chitnis T, Weiner HL, Khoury SJ. Evaluation of circulating osteopontin levels in an unselected cohort of patients with multiple sclerosis: Relevance for biomarker development. *Multiple Sclerosis*. 2014;**20**:438-444. DOI: 10.1177/1352458513503052
- [55] Runia TF, van Meurs M, Nasserinejad K, Hintzen RQ. No evidence for an association of osteopontin plasma levels with disease activity in multiple sclerosis. *Multiple Sclerosis*. 2014;**20**:1670-1671. DOI: 10.1177/1352458514528765
- [56] Niino M, Kikuchi S, Fukazawa T, Yabe I, Tashiro K. Genetic polymorphisms of osteopontin in association with multiple sclerosis in Japanese patients. *Journal of Neuroimmunology*. 2003;**136**:125-129
- [57] Caillier S, Barcellos LF, Baranzini SE, Swerdlin A, Lincoln RR, Steinman L, Martin E, Haines JL, Pericak-Vance M, Hauser SL, Oksenberg JR. Osteopontin polymorphisms and disease course in multiple sclerosis. *Genes and Immunity*. 2003;**4**:312-315. DOI: 10.1038/sj.gene.6363952
- [58] Hensiek AE, Roxburgh R, Meranian M, Seaman S, Yeo T, Compston DA, Sawcer SJ. Osteopontin gene and clinical severity of multiple sclerosis. *Journal of Neurology*. 2003;**250**:943-947. DOI: 10.1007/s00415-003-1120-2
- [59] Chiochetti A, Indelicato M, Bensi T, Mesturini R, Giordano M, Sametti S, Castelli L, Bottarel F, Mazzarino MC, Garbarini L, Giacobelli F, Valesini G, Santoro C, Dianzani I, Ramenghi U, Dianzani U. High levels of osteopontin associated with polymorphisms in its gene are a risk factor for development of autoimmunity/lymphoproliferation. *Blood*. 2004;**103**:1376-1382. DOI: 10.1182/blood-2003-05-1748
- [60] Chiochetti A, Comi C, Indelicato M, Castelli L, Mesturini R, Bensi T, Mazzarino MC, Giordano M, D'Alfonso S, Momigliano-Richiardi P, Liguori M, Zorzon M, Amoroso A, Trojano M, Monaco F, Leone M, Magnani C, Dianzani U. Osteopontin gene haplotypes correlate with multiple sclerosis development and progression. *Journal of Neuroimmunology*. 2005;**163**:172-178. DOI: 10.1016/j.jneuroim.2005.02.020
- [61] Comi C, Cappellano G, Chiochetti A, Orilieri E, Buttini S, Ghezzi L, Galimberti D, Guerini F, Barizzone N, Perla F, Leone M, D'Alfonso S, Caputo D, Scarpini E, Cantello R, Dianzani U. The impact of osteopontin gene variations on multiple sclerosis development and progression. *Clinical and Developmental Immunology*. 2012;**2012**:212893. DOI: 10.1155/2012/212893
- [62] Carmona L, Cross M, Williams B, Lassere M, March L. Rheumatoid arthritis. *Best Practice and Research: Clinical Rheumatology*. 2010;**24**:733-745. DOI: 10.1016/j.berh.2010.10.001

- [63] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *The New England Journal of Medicine*. 2011;**365**:2205-2219. DOI: 10.1056/NEJMra1004965
- [64] Petrow PK, Hummel KM, Schedel J, Franz JK, Klein CL, Müller-Ladner U, Kriegsmann J, Chang PL, Prince CW, Gay RE, Gay S. Expression of osteopontin messenger RNA and protein in rheumatoid arthritis: Effects of osteopontin on the release of collagenase 1 from articular chondrocytes and synovial fibroblasts. *Arthritis and Rheumatism*. 2000;**43**:1597-1605. DOI: 10.1002/1529-0131(200007)43:7<1597::AID-ANR25>3.0.CO;2-0
- [65] Shio K, Kobayashi H, Asano T, Saito R, Iwadate H, Watanabe H, Sakuma H, Segawa T, Maeda M, Ohira H. Thrombin-cleaved osteopontin is increased in urine of patients with rheumatoid arthritis. *The Journal of Rheumatology*. 2010;**37**:704-710. DOI: 10.3899/jrheum.090582
- [66] Xu G, Sun W, He D, Wang L, Zheng W, Nie H, Ni L, Zhang D, Li N, Zhang J. Overexpression of osteopontin in rheumatoid synovial mononuclear cells is associated with joint inflammation, not with genetic polymorphism. *The Journal of Rheumatology*. 2005;**32**:410-416
- [67] Zheng W, Li R, Pan H, He D, Xu R, Guo TB, Guo Y, Zhang JZ. Role of osteopontin in induction of monocyte chemoattractant protein 1 and macrophage inflammatory protein 1beta through the NF-kappaB and MAPK pathways in rheumatoid arthritis. *Arthritis and Rheumatism*. 2009;**60**:1957-1965. DOI: 10.1002/art.24625
- [68] Iwadate H, Kobayashi H, Kanno T, Asano T, Saito R, Sato S, Suzuki E, Watanabe H, Ohira H. Plasma osteopontin is correlated with bone resorption markers in rheumatoid arthritis patients. *International Journal of Rheumatoid Diseases*. 2014;**17**:50-56. DOI: 10.1111/1756-185X.12115
- [69] Urcelay E, Martínez A, Mas-Fontao A, Peris-Pertusa A, Pascual-Salcedo D, Balsa A, Fernández-Arquero M, de la Concha E. Osteopontin gene polymorphisms in Spanish patients with rheumatoid arthritis. *The Journal of Rheumatology*. 2005;**32**:405-409
- [70] Ceccarelli F, D'Alfonso S, Perricone C, Carlomagno Y, Alessandri C, Croia C, Barizzone N, Montecucco C, Galeazzi M, Sebastiani GD, Minisola G, Fiocco U, Valesini. The role of eight polymorphisms in three candidate genes in determining the susceptibility, phenotype, and response to anti-TNF therapy in patients with rheumatoid arthritis. *Clinical and Experimental Rheumatology*. 2012;**30**:939-942
- [71] Gazal S, Sacre K, Allanore Y, Teruel M, Goodall AH, Tohma S, Alfredsson L, Okada Y, Xie G, Constantin A, Balsa A, Kawasaki A, Nicaise P, Amos C, Rodriguez-Rodriguez L, Chiochia G, Boileau C, Zhang J, Vittecoq O, Barnetche T, Gonzalez Gay MA, Furukawa H, Cantagrel A, Le Loët X, Sumida T, Hurtado-Nedelec M, Richez C, Chollet-Martin S, Schaeffer T, Combe B, Khoryati L, Coustet B, El-Benna J, Siminovitch K, Plenge R, Padyukov L, Martin J, Tsuchiya N, Dieudé P. Identification of secreted phosphoprotein 1 gene as a new rheumatoid arthritis susceptibility gene. *Annals of the Rheumatic Diseases*. 2015;**74**:e19. DOI: 10.1136/annrheumdis-2013-204581
- [72] Juge PA, van Steenberg HW, Constantin A, Tobon GJ, Schaeffer T, Gazal S, Combe B, Devauchelle-Pensec V, Nigon D, van der Helm-van Mil AH, Dieudé P. SPP1

- rs9138 variant contributes to the severity of radiological damage in anti-citrullinated protein autoantibody-negative rheumatoid arthritis. *Annals of the Rheumatic Diseases*. 2014;**73**:1840-1843. DOI: 10.1136/annrheumdis-2014-205539
- [73] Ferri C, Sebastiani M, Lo Monaco A, Iudici M, Giuggioli D, Furini F, Manfredi A, Cuomo G, Spinella A, Colaci M, Govoni M, Valentini G. Systemic sclerosis evolution of disease pathomorphosis and survival. Our experience on Italian patients' population and review of the literature. *Autoimmunity Reviews*. 2014;**13**:1026-1034. DOI: 10.1016/j.autrev.2014.08.029
- [74] Chizzolini C, Brembilla NC, Montanari E, Truchetet ME. Fibrosis and immune dysregulation in systemic sclerosis. *Autoimmunity Reviews*. 2011;**10**:276-281. DOI: 10.1016/j.autrev.2010.09.016
- [75] Fuschiotti P. Current perspectives on the immunopathogenesis of systemic sclerosis. *Immunotargets and Therapy*. 2016;**5**:21-35. DOI: 10.2147/ITT.S82037
- [76] Geyer M, Müller-Ladner U. The pathogenesis of systemic sclerosis revisited. *Clinical Reviews in Allergy & Immunology*. 2011;**40**:92-103. DOI: 10.1007/s12016-009-8193-3
- [77] Collins AR, Schnee J, Wang W, Kim S, Fishbein MC, Bruemmer D, Law RE, Nicholas S, Ross RS, Hsueh WA. Osteopontin modulates angiotensin II-induced fibrosis in the intact murine heart. *Journal of the American College of Cardiology*. 2004;**43**:1698-1705. DOI: 10.1016/j.jacc.2003.11.058
- [78] Wolak T, Kim H, Ren Y, Kim J, Vaziri ND, Nicholas SB. Osteopontin modulates angiotensin II-induced inflammation, oxidative stress, and fibrosis of the kidney. *Kidney International*. 2009;**76**:32-43. DOI: 10.1038/ki.2009.90
- [79] Lorenzen JM, Krämer R, Meier M, Werfel T, Wichmann K, Hoepfer MM, Riemekasten G, Becker MO, Haller H, Witte T. Osteopontin in the development of systemic sclerosis—Relation to disease activity and organ manifestation. *Rheumatology (Oxford)*. 2010;**49**:1989-1991. DOI: 10.1093/rheumatology/keq223
- [80] Corallo C, Volpi N, Franci D, Montella A, Biagioli M, Mariotti G, D'Onofrio F, Gonnelli S, Nuti R, Giordano N. Is osteopontin involved in cutaneous fibroblast activation? Its hypothetical role in scleroderma pathogenesis. *International Journal of Immunopathology and Pharmacology*. 2014;**27**:97-102
- [81] Wu M, Schneider DJ, Mayes MD, Assassi S, Arnett FC, Tan FK, Blackburn MR, Agarwal SK. Osteopontin in systemic sclerosis and its role in dermal fibrosis. *The Journal of Investigative Dermatology*. 2012;**132**:1605-1614. DOI: 10.1038/jid.2012.32
- [82] Barizzone N, Marchini M, Cappiello F, Chiocchetti A, Orilieri E, Ferrante D, Corrado L, Mellone S, Scorza R, Dianzani U, D'Alfonso S. Association of osteopontin regulatory polymorphisms with systemic sclerosis. *Human Immunology*. 2011;**72**:930-934. DOI: 10.1016/j.humimm.2011.06.009

- [83] Baumgart DC, Sandborn WJ. Inflammatory bowel disease: Clinical aspects and established and evolving therapies. *Lancet*. 2007;**369**:1641-1657. DOI: 10.1016/S0140-6736(07)60751-X
- [84] Sands BE. From symptom to diagnosis: Clinical distinctions among various forms of intestinal inflammation. *Gastroenterology*. 2004;**126**:1518-1532. DOI: 10.1053/j.gastro.2004.02.072
- [85] Silva FA, Rodrigues BL, Ayrizono ML, Leal RF. The immunological basis of inflammatory bowel disease. *Gastroenterology Research and Practice*. 2016;**2016**:2097274. DOI: 10.1155/2016/2097274
- [86] Heilmann K, Hoffmann U, Witte E, Loddenkemper C, Sina C, Schreiber S, Hayford C, Holzlohner P, Wolk K, Tchatchou E, Moos V, Zeitz M, Sabat R, Günthert U, Wittig BM. Osteopontin as two-sided mediator of intestinal inflammation. *Journal of Cellular and Molecular Medicine*. 2009;**13**:1162-1174. DOI: 10.1111/j.1582-4934.2008.00428.x
- [87] Gassler N, Autschbach F, Gauer S, Bohn J, Sido B, Otto HF, Geiger H, Obermüller N. Expression of osteopontin (Eta-1) in Crohn disease of the terminal ileum. *Scandinavian Journal of Gastroenterology*. 2002;**37**:1286-1295
- [88] Masuda H, Takahashi Y, Asai S, Takayama T. Distinct gene expression of osteopontin in patients with ulcerative colitis. *The Journal of Surgical Research*. 2003;**111**:85-90
- [89] Sato T, Nakai T, Tamura N, Okamoto S, Matsuoka K, Sakuraba A, Fukushima T, Uede T, Hibi T. Osteopontin/Eta-1 upregulated in Crohn's disease regulates the Th1 immune response. *Gut*. 2005;**54**:1254-1262. DOI: 10.1136/gut.2004.048298
- [90] Mishima R, Takeshima F, Sawai T, Ohba K, Ohnita K, Isomoto H, Omagari K, Mizuta Y, Ozono Y, Kohno S. High plasma osteopontin levels in patients with inflammatory bowel disease. *Journal of Clinical Gastroenterology*. 2007;**41**:167-172. DOI: 10.1097/MCG.0b013e31802d6268
- [91] Komine-Aizawa S, Masuda H, Mazaki T, Shiono M, Hayakawa S, Takayama T. Plasma osteopontin predicts inflammatory bowel disease activities. *International Surgery*. 2015;**100**:38-43. DOI: 10.9738/INTSURG-D-13-00160.1
- [92] Agnholt J, Kelsen J, Schack L, Hvas CL, Dahlerup JF, Sørensen ES. Osteopontin, a protein with cytokine-like properties, is associated with inflammation in Crohn's disease. *Scandinavian Journal of Immunology*. 2007;**65**:453-460. DOI: 10.1111/j.1365-3083.2007.01908.x
- [93] Tang R, Yang G, Zhang S, Wu C, Chen M. Opposite effects of interferon regulatory factor 1 and osteopontin on the apoptosis of epithelial cells induced by TNF- $\alpha$  in inflammatory bowel disease. *Inflammatory Bowel Disease*. 2014;**20**:1950-1961. DOI: 10.1097/MIB.0000000000000192
- [94] Chen F, Liu H, Shen Q, Yuan S, Xu L, Cai X, Lian J, Chen SY. Osteopontin: Participation in inflammation or mucosal protection in inflammatory bowel diseases? *Digestive Diseases and Sciences*. 2013;**58**:1569-1580. DOI: 10.1007/s10620-012-2556-y

- [95] Zhong J, Eckhardt ER, Oz HS, Bruemmer D, de Villiers WJ. Osteopontin deficiency protects mice from Dextran sodium sulfate-induced colitis. *Inflammatory Bowel Diseases*. 2006;**12**:790-796
- [96] da Silva AP, Pollett A, Rittling SR, Denhardt DT, Sodek J, Zohar R. Exacerbated tissue destruction in DSS-induced acute colitis of OPN-null mice is associated with downregulation of TNF-alpha expression and non-programmed cell death. *Journal of Cellular Physiology*. 2006;**208**:629-639
- [97] da Silva AP, Ellen RP, Sørensen ES, Goldberg HA, Zohar R, Sodek J. Osteopontin attenuation of dextran sulfate sodium-induced colitis in mice. *Laboratory Investigation*. 2009;**89**:1169-1181. DOI: 10.1038/labinvest.2009.80
- [98] Toyonaga T, Nakase H, Ueno S, Matsuura M, Yoshino T, Honzawa Y, Itou A, Namba K, Minami N, Yamada S, Koshikawa Y, Uede T, Chiba T, Okazaki K. Osteopontin deficiency accelerates spontaneous colitis in mice with disrupted gut microbiota and macrophage phagocytic activity. *PLoS One*. 2015;**10**:e0135552. DOI: 10.1371/journal.pone.0135552
- [99] Kanwar JR, Kanwar RK, Stathopoulos S, Haggarty NW, MacGibbon AK, Palmano KP, Roy K, Rowan A, Krissansen GW. Comparative activities of milk components in reversing chronic colitis. *Journal of Dairy Science*. 2016;**99**:2488-2501. DOI: 10.3168/jds.2015-10122
- [100] Glas J, Seiderer J, Bayrle C, Wetzke M, Fries C, Tillack C, Olszak T, Beigel F, Steib C, Friedrich M, Diegelmann J, Czamara D, Brand S. The role of osteopontin (OPN/SPP1) haplotypes in the susceptibility to Crohn's disease. *PLoS One*. 2011;**6**:e29309. DOI: 10.1371/journal.pone.0029309
- [101] Schranz DB, Lernmark A. Immunology in diabetes: An update. *Diabetes/Metabolism Reviews*. 1998;**14**:3-29
- [102] Daneman D. Type 1 diabetes. *Lancet*. 2006;**367**:847-858. DOI: 10.1016/S0140-6736(06)68341-4
- [103] Ahlqvist E, Osmark P, Kuulasmaa T, Pilgaard K, Omar B, Brons C, Kotova O, Zetterqvist AV, Stancakova A, Jonsson A, Hansson O, Kuusisto J, Kieffer TJ, Tuomi T, Isomaa B, Madsbad S, Gomez MF, Poulsen P, Laakso M, Degerman E, Pihlajamäki J, Wierup N, Vaag A, Groop L, Lyssenko V. Link between GIP and osteopontin in adipose tissue and insulin resistance. *Diabetes*. 2013;**62**:2088-2094. DOI: 10.2337/db12-0976
- [104] Talat MA, Sherief LM, El-Saadany HF, Rass AA, Saleh RM, Sakr MM. The role of osteopontin in the pathogenesis and complications of type 1 diabetes mellitus in children. *Journal of Clinical Research in Pediatric Endocrinology*. 2016;**8**:399-404. DOI: 10.4274/jcrpe.3082
- [105] Karamizadeh Z, Kamali Sarvestani E, Saki F, Karamifar H, Amirhakimi GH, Namavar Shooshtarian MH, Ashkani-Esfahani S. Investigation of osteopontin levels and genomic variation of osteopontin and its receptors in Type 1 diabetes mellitus. *Journal of Endocrinological Investigation*. 2013;**36**:1090-1093. DOI: 10.3275/9098

- [106] Barchetta I, Alessandri C, Bertocchini L, Cimini FA, Taverniti L, Di Franco M, Fraioli A, Baroni MG, Cavallo MG. Increased circulating osteopontin levels in adult patients with type 1 diabetes mellitus and association with dysmetabolic profile. *European Journal of Endocrinology*. 2016;**174**:187-192. DOI: 10.1530/EJE-15-0791
- [107] Gordin D, Forsblom C, Panduru NM, Thomas MC, Bjerre M, Soro-Paavonen A, Tolonen N, Sandholm N, Flyvbjerg A, Harjutsalo V, Groop PH; FinnDiane Study Group. Osteopontin is a strong predictor of incipient diabetic nephropathy, cardiovascular disease, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care*. 2014;**37**:2593-2600. DOI: 10.2337/dc14-0065
- [108] Marciano R, D'Annunzio G, Minuto N, Pasquali L, Santamaria A, Di Duca M, Ravazzolo R, Lorini R. Association of alleles at polymorphic sites in the Osteopontin encoding gene in young type 1 diabetic patients. *Clinical Immunology*. 2009;**131**:84-91. DOI: 10.1016/j.clim.2008.11.004
- [109] Chiocchetti A, Orilieri E, Cappellano G, Barizzzone N, D'Alfonso S, D'Annunzio G, Lorini R, Ravazzolo R, Cadario F, Martinetti M, Calcaterra V, Cerutti F, Bruno G, Larizza D, Dianzani U. The osteopontin gene +1239A/C single nucleotide polymorphism is associated with type 1 diabetes mellitus in the Italian population. *International Journal of Immunopathology and Pharmacology*. 2010;**23**:263-269
- [110] Lloyd CM, Hessel EM. Functions of T cells in asthma: More than just T(H)2 cells. *Nature Reviews. Immunology*. 2010;**10**:838-848. DOI: 10.1038/nri2870
- [111] Dunican EM, Fahy JV. The role of Type 2 inflammation in the pathogenesis of asthma exacerbations. *Annals of the American Thoracic Society*. 2015;**12**(Suppl 2):S144-S149. DOI:10.1513/AnnalsATS.201506-377AW
- [112] Kay AB. The role of T lymphocytes in asthma. *Chemical Immunology and Allergy*. 2006;**91**:59-75. DOI: 10.1159/000090230
- [113] Xanthou G, Alissafi T, Semitekolou M, Simoes DC, Economidou E, Gaga M, Lambrecht BN, Lloyd CM, Panoutsakopoulou V. Osteopontin has a crucial role in allergic airway disease through regulation of dendritic cell subsets. *Nature Medicine*. 2007;**13**:570-578. DOI: 10.1038/nm1580
- [114] Samitas K, Zervas E, Xanthou G, Panoutsakopoulou V, Gaga M. Osteopontin is increased in the bronchoalveolar lavage fluid and bronchial tissue of smoking asthmatics. *Cytokine*. 2013;**61**:713-715. DOI: 10.1016/j.cyto.2012.12.028
- [115] Takahashi A, Kurokawa M, Konno S, Ito K, Kon S, Ashino S, Nishimura T, Uede T, Hizawa N, Huang SK, Nishimura M. Osteopontin is involved in migration of eosinophils in asthma. *Clinical and Experimental Allergy*. 2009;**39**:1152-1159. DOI: 10.1111/j.1365-2222.2009.03249.x
- [116] Yang AM, Huang R, Jin SJ. ORMDL3 polymorphisms and their relationship with OPN and TGF- $\beta$ 1 levels in children with asthma in Hunan, China: An analysis of 98 cases. *Chinese Journal of Contemporary Pediatrics*. 2016;**18**:324-328. Chinese

- [117] Haagerup A, Bjerke T, Schøitz PO, Binderup HG, Dahl R, Kruse TA. Allergic rhinitis—A total genome-scan for susceptibility genes suggests a locus on chromosome 4q24-q27. *European Journal of Human Genetics*. 2001;**9**:945-952. DOI: 10.1038/sj.ejhg.5200753
- [118] Tanino Y, Hizawa N, Konno S, Fukui Y, Takahashi D, Maeda Y, Huang SK, Nishimura M. Sequence variants of the secreted phosphoprotein 1 gene are associated with total serum immunoglobulin E levels in a Japanese population. *Clinical and Experimental Allergy*. 2006;**36**:219-225. DOI: 10.1111/j.1365-2222.2006.02414.x
- [119] Arjomandi M, Galanter JM, Choudhry S, Eng C, Hu D, Beckman K, Chapela R, Rodríguez-Santana JR, Rodríguez-Cintrón W, Ford J, Avila PC, Burchard EG. Polymorphism in osteopontin gene (SPP1) is associated with asthma and related phenotypes in a Puerto Rican population. *Pediatric Allergy, Immunology, and Pulmonology*. 2011;**24**:207-214. DOI: 10.1089/ped.2011.0095
- [120] Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. *Lancet*. 2014;**383**:1155-1167. DOI: 10.1016/S0140-6736(13)60680-7
- [121] James DG, Neville E, Siltzbach LE. A worldwide review of sarcoidosis. *Annals of the New York Academy of Sciences*. 1976;**278**:321-334
- [122] Carlson I, Tognazzi K, Manseau EJ, Dvorak HF, Brown LF. Osteopontin is strongly expressed by histiocytes in granulomas of diverse etiology. *Laboratory Investigation*. 1997;**77**:103-108
- [123] O'Regan AW, Chupp GL, Lowry JA, Goetschkes M, Mulligan N, Berman JS. Osteopontin is associated with T cells in sarcoid granulomas and has T cell adhesive and cytokine-like properties in vitro. *Journal of Immunology*. 1999;**162**:1024-1031
- [124] Maeda K, Takahashi K, Takahashi F, Tamura N, Maeda M, Kon S, Uede T, Fukuchi Y. Distinct roles of osteopontin fragments in the development of the pulmonary involvement in sarcoidosis. *Lung*. 2001;**179**:279-291. DOI: 10.1007/s004080000068
- [125] Akahoshi M, Ishihara M, Remus N, Uno K, Miyake K, Hirota T, Nakashima K, Matsuda A, Kanda M, Enomoto T, Ohno S, Nakashima H, Casanova JL, Hopkin JM, Tamari M, Mao XQ, Shirakawa T. Association between IFNA genotype and the risk of sarcoidosis. *Human Genetics*. 2004;**114**:503-509. DOI: 10.1007/s00439-004-1099-5
- [126] Maver A, Medica I, Salobir B, Tercelj M, Peterlin B. Genetic variation in osteopontin gene is associated with susceptibility to sarcoidosis in Slovenian population. *Disease Markers*. 2009;**27**:295-302. DOI: 10.3233/DMA-2009-0675