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Original Article

A clinical review of autoinflammatory diseases and Behcet's disease: Classification, pathogenesis and treatment

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ABSTRACT

Behcet's disease is a rheumatic disease with oral aphthae, genital aphthae, arthritis and vasculitis. Studies about its pathogenesis have increased and is thought to be one of the autoinflammatory diseases in recent years. Autoinflammatory diseases occurs via excess response of innate immune system. In this article pathogenesis and classification of autoinflammatory diseases will be summarized and Behcet's disease will be reviewed by autoinflammatory prospects.

Keywords: Autoinflammatory disease, Behcet's disease, innate immune system.

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Introduction

Autoinflammatory diseases are episodic conditions that occur via excess response of innate immune system and cause fever and inflammation in many organs. Awareness of autoinflammatory diseases rose after definition of tumor necrosis receptor associated periodic syndrome (TRAPS) in 1999 by McDermott [1]. Advances in recognition of these diseases were developed in recent 20 years by increased awareness of this kind of conditions and by advances in genetic science. Treatment of these disease was advanced by therapies which target innate immune system. Autoinflammation is predominant in the pathogenesis of these conditions and may be together with autoimmunity. Autoinflammation is different from autoimmunity by which the innate immune system is responsible from autoinflammation where B lymphocyte and other acquired immune system cells and cytokines are active in the latter. Therefore, disease specific antibody develops and be detected in autoimmunity, however, neither antibodies related to organ damage nor antigen specific t lymphocytes were detectable in autoinflammation [2]. Figure 1 shows these conditions and their pathogenesis.

Familial Mediterranean Fever (FMF) is the first autoinflammatory disease which was associated with genetics. Following this development, TNFRSF1 gene mutation was determined in TRAPS. Clinical findings of both diseases include episodic sterile inflammation, fever, myositis, arthralgia, rash-like rashes on the skin and serositis. The absence of any autoantibody and auto-reactive T cell positivity has led clinical research to focus on the innate

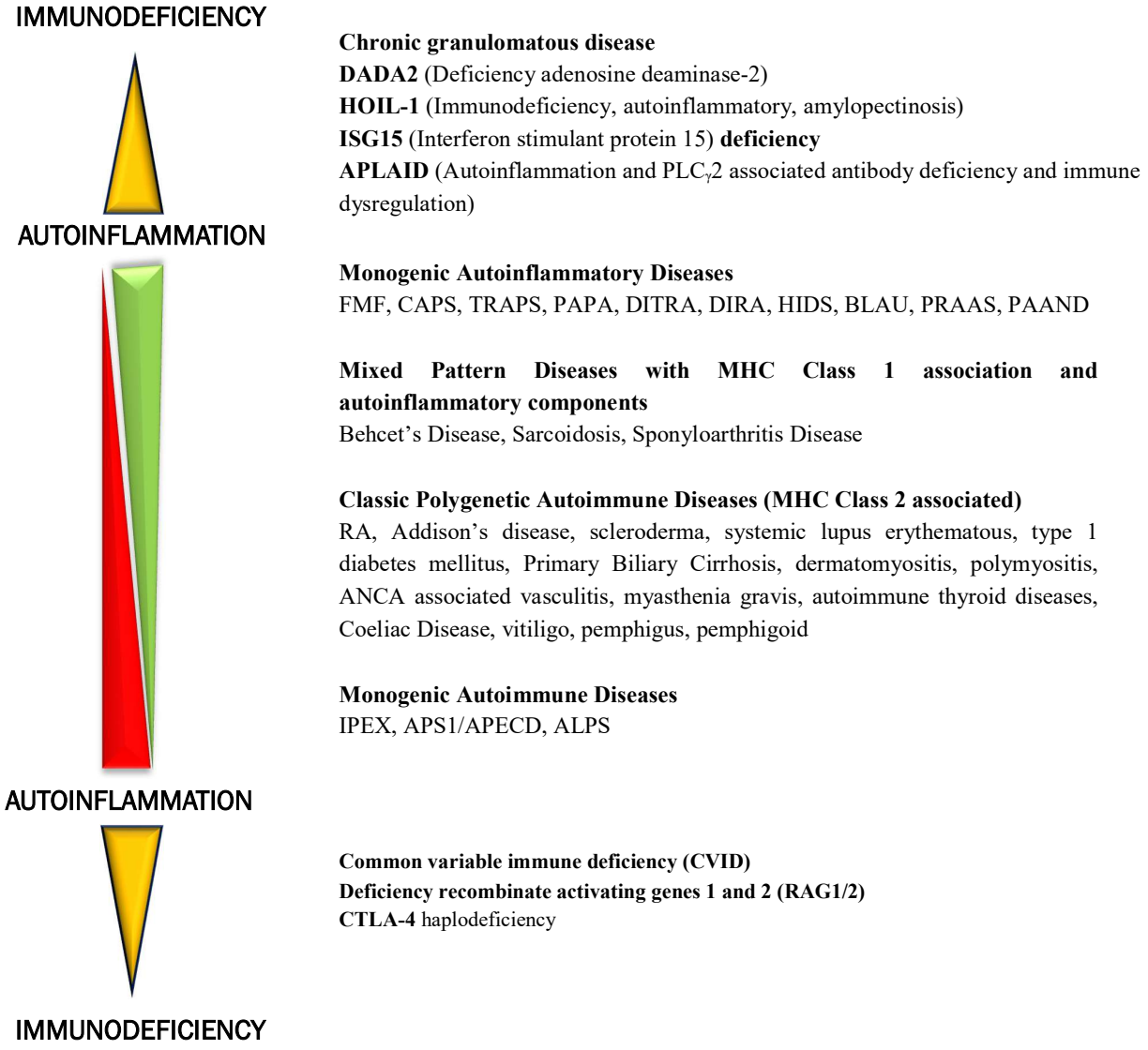

Figure 1. The spectrum of autoinflammatory diseases, FMF: Familial Mediterranean fever; TRAPS: Tumor necrosis factor receptor associated periodic syndrome; CAPS: Cryopyrin-associated periodic syndrome; HIDS: Hyperimmunoglobulin D Syndrome; PAPA: Pyogenic arthritis, pyoderma gangrenosum, acne; DIRA: Deficiency of the interleukin-1–receptor antagonist; PAAND: Pyrin associated autoinflammation with neutrophilic dermatosis; PRAAS: Proteasome-associated autoinflammatory syndromes; AOSD: Adult's still syndrome; R.A: Rheumatoid arthritis; ALPS: Autoimmune lymphoproliferative syndrome; APS-1: autoimmune polyendocrine syndrome type 1 of APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy); IPEX: immunodysregulation polyendocrinopathy enteropathy X-linked syndrome [2].

immune system and possibly related gene studies [3]. In present study, pathogenesis and classification of autoinflammatory diseases will be summarized and Behcet's disease will be reviewed by autoinflammatory prospects.

Pathogenesis of autoinflammatory diseases

The innate immune system is responsible of the first and fastest response to inflammation. This response is not antigen specific but consists of several cells and cytokines. The first cytokines

released as the innate immune system activated are interleukin-1 (IL-1), IL-8, tumor necrosis factor alpha (TNFα) and type 1 interferons (IFNα and IFNβ).

Inflammasome

It is the signaling complex that provides the intracellular response of the innate immune system which was first described in 2002. Some cytosolic receptors in inflammasome formation include absent in melanoma-2 (AIM2), recombinant activation gene-1 (RAG-1), pyrin and most importantly NOD like receptor family (NLR) which includes NLRP3. It is schematized in Figure-2 [4].

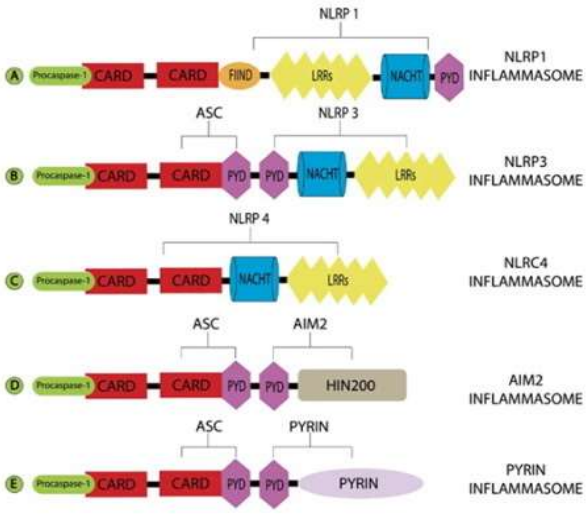

Figure 2. Inflammasome related cytoplasmic receptors [4].

In the stimulation of cytosolic receptors, apoptosis-associated speck-like protein-containing CARD (ASC) plays a role, acting as an adapter protein, cooperating in all inflammasomes. This step is organized by the inflammasome complex. It converts Procaspase-1, to the active form caspase-1 and stimulates the proinflammatory cytokines (pro-IL-1β and pro-IL-18) to turn into their active forms. There are several factors that stimulate both endogenous and exogenous inflammasomes. An example of exogenous stimulants is pathogen-related molecular patterns (PAMPs). Lipopolysaccharides in gram-negative bacteria cell wall, lipoteichoic acid in gram-positive bacteria, double-stranded RNA viruses, peptidoglycan, flagellin are some of the PAMPs. Endogenous factors include nucleus and cytosolic proteins, that occurred during cell-death and damage-associated molecular patterns (DAMPS), which reacts to potential cancer cells and remove cellular residues [3]. Activation of inflammasome is critical for the innate immune system, and genetic mutations at this stage cause uncontrolled activations, leading to autoinflammatory diseases.

Interleukin -1β (IL - 1β) and IL - 18

IL-1β was detected before the identification of inflammasome. It is an acute phase reactant and a pyrogen. It is released from macrophages, dentritic cells, neutrophils and keratinocytes. It is activated by the IL-1 receptor type I (IL-1R) and stimulates the nuclear factor kappa light-chain-enhancer of activate B cell (NFκB) and causes expression of cyclooxygenase-2. It also provides the release of IL-6 and TNF-α and cause fever. Under normal conditions, it is released during infections and initiates inflammation against the pathogens. Pathologically excessive stimulation or formation causes autoinflammation. Effects of IL-1α plays a role via IL-1R in healthy individuals and has a very low importance in autoinflammation [6]. In contrast, inhibitory drugs developed against IL-1β provided an important clinical response in the treatment of autoinflammatory diseases [7].

Information on IL-18 is less than IL-1β. It plays a role as IFN-γ and proinflammatory cytokines. Its role in fever formation and as an acute phase reactant is weak. It has a role in inflammatory

Table 1. Monogenetic autoinflammatory diseases [10].

Monogenic autoinflammatory conditions	Gene (protein)	Clinic Manifestations	Treatment
Familial Mediterranean fever (FMF)	MEFV (pyrin)	Fever, abdominal pain, arthritis, erysipelas-like skin rashes	Colchicine, canakinumab, anakinra, rilonacept, TNF inhibitors
Cryoporin-associated periodic syndromes (CAPS)	NLRP3 (cryoporin)	Fever, conjunctivitis, arthritis, urticaria	Anakinra, rilonacept, canakinumab, steroid, NSAIDs
Mevalonate kinase deficiency (MKD)	MVK (mevalonate kinase)	Fever, severe abdominal pain, diarrhea, arthralgia, rash, lymphadenopathy, splenomegaly,	Corticosteroids, NSAIDs, anakinra, canakinumab, TNF inhibitors
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	TNFRSF1A (TNF receptor type 1)	Fever, myalgia, abdominal pain, conjunctivitis	Corticosteroids, NSAIDs, canakinumab, anakinra, etanercept
Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome	PSTPIP1 (proline/serine/threonine/ phosphatase-interacting protein)	Erosive arthritis, pyoderma gangrenosum, acne	Corticosteroids, anakinra, canakinumab, infliximab, adalimumab
Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)	MEFV (pyrin)	Fever, arthralgia, myositis, neutrophilic dermatosis	Anakinra, infliximab, adalimumab
Blau's syndrome (familial juvenile systemic granulomatosis)	NOD2 (nucleotide-binding oligomerization domain-containing protein 2)	granulomatous reactions, tenosynovitis, uveitis	Corticosteroids, methotrexate, cyclosporin, TNF inhibitors, anakinra
Deficiency of the IL-1 receptor antagonist (DIRA)	IL1RN (IL-1 receptor antagonist)	Osteomyelitis, osteopenia, periostitis, pustular dermatitis	Anakinra, canakinumab, rilonacept
Deficiency of the IL-36 receptor antagonist (DITRA)	IL36RN (IL-36 receptor antagonist)	Fever, neutrophilia, pustular psoriasis	Acitretin, corticosteroids, TNF inhibitors, methotrexate, cyclosporine, phototherapy
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome	lipodystrophy and elevated temperature (CANDLE) syndrome PSMA3, PSMB4, PSMB8, PSMB9 (proteasome subunits)	Fever, progressive facial lipodystrophy, periorbital edema	JAK inhibition with baricitinib, methotrexate, corticosteroids, cyclosporine, azathioprine, IVIG
STING-associated vasculopathy with onset in infancy (SAVI)	TMEM173 (STING)	Acral vasculitis increasing with cold, pustular lesions	Baricitinib, tofacitinib, ruxolitinib, corticosteroid

IL: Interleukin, IVIG: Intravenous immunoglobulin, JAK: Janus Kinase NSAIDs: Nonsteroidal anti-inflammatory drug; STING: Stimulator of interferon gene; TNF: Tumor necrosis factor.

Table 2. Multifactorial autoinflammatory diseases [10].

Multifactorial autoinflammatory C	Genes	Clinic Manifestation	Treatment
Hidradenitis suppurativa (HS)	Unknown	Nodules with ulceration, abscesses, and fistulas; evolve into hypertrophic scars	Adalimumab, infliximab, ustekinumab, anakinra, antibiotics, corticosteroids
Generalized pustular psoriasis (GPP)	CARD14, IL36RN	Widespread subcorneal pustules overlying erythematous plaques	Retinoids, cyclosporine, methotrexate, infliximab, gevokizumab, canakinumab, IL-17A inhibitors
Palmoplantar pustular psoriasis (PPPP)	CARD14	Sterile pustules on palms and soles; hyperkeratosis and fissuring	PUVA, UVB, acitretin, methotrexate, corticosteroids, cyclosporine, ustekinumab
Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO)	PSTPIP2, LPIN2, NOD2, IL1RN, unknown	Osteomyelitis, hyperostosis, synovitis, acne, fissure	NSAIDs, methotrexate, sulfasalazine, bisphosphonates, TNF inhibitors, ustekinumab, secukinumab, anakinra
Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)	PSTPIP1, NLRP3, MEFV, NOD2, PSMB8, NCSTN	Suppurative hidradenitis; acne; pyoderma gangrenosum later	Anakinra, infliximab, adalimumab
Behcet's disease (BD)	MEFV, HLA-B51, TNFAIP3, complex	Oral aphthous ulcers; genital ulcers; erythema nodosum, vasculitis	Colchicine, corticosteroids, azathioprine, thalidomide, cyclosporine, anakinra, cyclophosphamide, TNF inhibitors, canakinumab, tocilizumab
Systemic juvenile idiopathic arthritis (SJIA)	Complex	Maculopapular rash, arthritis, fever, serositis, hepatosplenomegaly	Corticosteroids, NSAIDs, canakinumab, anakinra, tocilizumab
Adult-onset Still's disease (AOSD)	Complex	Maculopapular rash, arthritis, fever, serositis, hepatosplenomegaly	Corticosteroids, DMARDs, TNF inhibitors, anakinra, canakinumab, tocilizumab
Schnitzler's syndrome	Unknown	Urticarial-like lesions with neutrophilic infiltrates, fever, arthritis, IgM gammopathy	Corticosteroids, anakinra, canakinumab, rilonacept
Sweet's syndrome (acute febrile neutrophilic dermatosis)	HLA-B54, PTPN6, IDH1, MEFV, unknown	Erythematous papules, nodules, and plaques, fever, leukocytosis	Corticosteroids, colchicine, dapsone, potassium iodide, anakinra, TNF inhibitors
Pyoderma gangrenosum (PG)	MEFV, NLRP3, NLRP12, NOD2, LPIN2, PSTPIP1, JAK2, MTHFR, complex.	Sterile pustules evolve into ulcers with undermined borders	Corticosteroids, antibiotics, IVIG, thalidomide, infliximab, ustekinumab, canakinumab, anakinra
Psoriasis	CARD14, IL36RN, TNFAIP3, TNIP1, unknown	Papules and plaques with silver scale, typically on extensor surfaces; sterile pustules; hyperkeratosis	Corticosteroids, retinoids, phototherapy, methotrexate, cyclosporine, TNF inhibitors, ustekinumab, secukinumab, ixekizumab, apremilast
Acne vulgaris	Complex	Comedones; papules; pustules; nodules; cysts	Antibiotics, retinoids, salicylic acid, spironolactone, nitric oxide-releasing .

DMARD: disease-modifying antirheumatic drug;IL: interleukin; IVIG: intravenous immunoglobulin; NSAIDs: nonsteroidal anti-infammatory drug; PUVA: psoralen and ultraviyolet- A; Anti-TNF:tumor necrosis factor inhibitör drug;UVB: ultraviyolet B; IgM: immunoglobulin M gamopathy.

bowel disease, heart disease, metabolic syndrome and malignancy. In mouse studies with malignant melanomas, IL-18 inhibition has been shown to reduce the development of vascular cell adhesion molecule-1 (VCAM-1), reducing the development of metastasis [8]. Thus, IL-18 inhibition strategies are targeted in both inflammatory diseases and cancer treatment.

Proteasome immunoproteasome

In some patient groups, the absence of clinical response with IL-1 inhibitory therapy and continued studies investigating the pathogenesis of the disease led to the identification of proteasome-immunoproteasome components. Proteasome-immunoproteasomes are several multiprotein structures that are responsible for the removal of intracellular and foreign cell waste. After recognition of the Type-1 IFN receptor by the cell surface, Janus Kinase (JAK) and the transluser and activator transcription factor (STAT) are stimulated. These all together cause increased production of IFN, formation of cell damage associated oxygen radicals and nitrogen proteins. These proteins are cleared from the cell by proteasomes and immune proteasomes in sake of cell survival [9].

Autoinflammatory diseases are divided into two either as monogenic autoinflammatory diseases or multifactorial autoinflammatory diseases, according to the detected genetic mutations. In monogenetic diseases, a single gene region has been associated with the disease while in multifactorial diseases, many gene mutations have been associated with the disease. Table-1 presents monogenetic autoinflammatory diseases and associated gene mutations and Table-2 presents multifactorial autoinflammatory diseases and related gene mutations [10].

Behcet's disease

Behcet's disease (BD) is included in the multifactorial autoinflammatory diseases group. Common clinical signs of autoinflammatory diseases include; oral aphthae, arthritis, papulopustular skin lesions, pathergy test positivity, uveitis, meningoencephalitis, genital aphthae, epididymoorchitis, lymphadenopathy and amyloidosis. Since the clinical findings of BH are similar to the clinical findings of autoinflammatory diseases, studies have been conducted on this subject, considering that BH could be an autoinflammatory disease. In table-3, the findings of BH that overlap with the clinic of autoinflammatory diseases are schematized [11].

Table 3. Clinical findings of Behcet's disease that overlap with autoinflammatory diseases [11].

Behcet's Disease's Clinic Finding	Autoinflammatory Diseases
Oral aphthous ulcers	MKD,TRAPS,CAPS
Skin pathergy reaction	PAPA
Arthritis	FMF,TRAPS, PAPA, Blau's Syndrome, CAPS, MKD
Papulopustuler/acne like lesions	DIRA, PAPA
Meningoencephalitis	FMF,CAPS
Uveitis	CAPS,TRAPS, Blau Syndrome
Genital aphthous ulcers	MKD
Orchyepididymitis	FMF
Amyloidosis	All autoinflammatory diseases

FMF: Familial Mediterranean fever; TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome; CAPS: Cryopyrin-associated periodic syndrome; PAPA: Pyogenic Arthritis, Pyoderma Gangrenosum, Acne; DIRA: Deficiency of the interleukin-1–receptor antagonist; MKD: Mevalonate kinase deficiency.

Pathogenesis of Behcet's disease

The over-activated natural immune response in BD triggers the release of T helper-1 and T cell 17 (Th17). Natural immune system cells are predominated in the early stage of the pathological findings of the disease [12]. Neutrophilic vasculitis is a well-established pathological finding in BD. Changes in T cell balance are in favor of an increase in Th1 / Th17 and a decrease in T regulator cell (Treg). Increased Th17 causes elevation of IL-17, IL-23 and IFN- γ. Increased neutrophil infiltration develops as this pathway becomes active [13]. Pathologies associated with BH are schematized in Figure-3 and 4 [14].

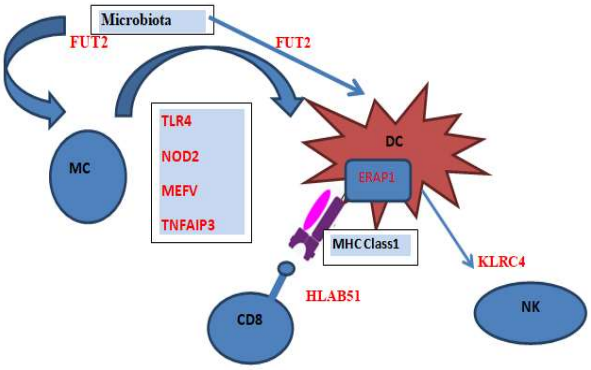

Figure 3. Immunopathology related to innate immune system in Behçet's disease (MC: Macrophages; DC: Dentritic cell; CD8: CD8 T cell; NK: Natural killer cell) [14].

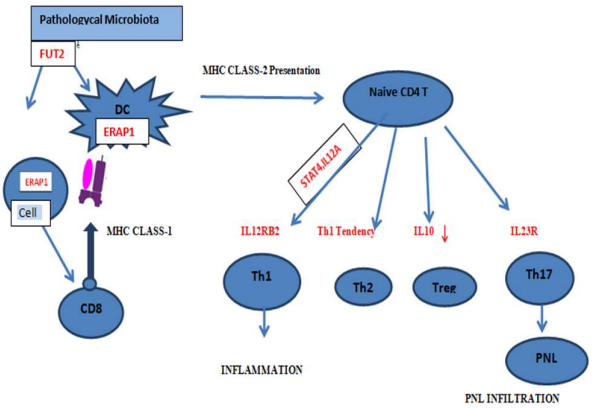

Figure 4. Immunopathology related to adaptive immune system in Behcet's Disease (DC: Dentritic cell; CD8: CD8 cytotoxic T cell; Th1:T helper1cell; Th2: Thelper2 cell; Treg: T regulatory cell; Th17:T 17 cell; PNL: neutrophils) [14].

On the other hand, there are studies showing that some microorganisms contribute to disease in susceptible individuals. Some streptococcal derivatives such as Streptococcus sanguinis, herpes simplex type-1 cause cross-reaction by showing homologous structure with human heat shock proteins (HSP) and have been shown to activate the immune system [15]. BH has been associated with microorganisms such as Borrelia burgdorferi, Helicobacter pylori, Cytomegalovirus, Epstein Barr virus, parvovirus, varicella zoster, but their relationship is unclear since these publications are consisted of few cases. Nevertheless, the role of microorganisms in disease pathogenesis is thought to be in the form of exacerbation of the disease [13,14].

Gene studies in Behcet's disease

Genetic studies conducted to elucidate Behcet's disease pathogenesis showed the presence of gene mutations associated with the natural immune system in this condition. Genetic mutation studies detected in BD are presented in Table 4 [14]. MEFV gene mutations are mutations detected in FMF patients and have also been detected in BD. However, the relationship of MEFV gene mutation with Behcet's Disease is not clear [16].

The genome region encoding IL10 is the first gene region detected in BD. Although different missense variants in this gene region differ among communities, some variants have been shown to be associated with BD [14]. These variations have been associated with the formation of autoinflammation by decreasing the release of IL-10 from macrophages and not showing the effect of IL-10 in limiting inflammation. There are studies showing that IL-10 level is lower in BD than healthy individuals [17].

Table 4. Gene studies of Behcet's disease [14].

Variant	Gene	Location	Function of the risk allele
rs1495965	IL23R,IL12RB2	Intergenic	
rs924080	IL23R,IL12RB2	Intergenic	
rs1518111	IL10	Intron	Reduces expression in monocytes
rs1800871	IL10	Promoter	
rs9494885	TNFAIP3	Intergenic	No difference in expression in PBMCs
rs7574070	STAT4	Intron	Increases expression
rs897200	STAT4	Intergenic	Increases expression of STAT4 and IL17
rs7616215	CCR1	Intergenic	Decreases expression in monocytes, reduces monocyte chemotaxis
rs13092160	CCR1, CCR3	Intergenic	Decreases expression in PBMCs
rs2617170	KLRC4	Missense	
M694V	MEFV	Missense	Increases response to LPS
rs17482078	ERAP1	Missense	
rs681343	FUT2	Synonymous	
rs17810546	IL12A	Intergenic	
R381Q,G149R	IL23R	Missense	Reduces IL-23 dependent IL-17
D299G, T399I	TLR4	Missense	Reduces response to LPS, hyporesponsiveness to endotoxin
R702W, G908R L1007fs	NOD2	Missense Frame shift	Reduces response to MDP

PBMC: Peripheral blood mononuclear cell; LPS: lipopolysaccharide; MDP: muramyl dipeptide.

Li et al. detected TNFAIP3 mutation in patients with 722 BH [18]. TNFAIP3 is the region encoding the ubiquitin modified enzyme A20. It plays an important regulatory role in the NF-kB signaling pathway and provides TNF, toll like receptors (TLRs), IL-1R and NOD2 release.

The p.Arg725Gln, variant gene in the ERAP1 gene has been studied and detected in the Turkish population, and found to be higher in patients with positive HLA B51 allele [19]. The fact that the disease is seen more in some geographical regions suggested that this variant may be due to mutations. ERAP1 encodes aminopeptidase-1 in the endoplasmic reticulum and contributes to the production of the N-terminal peptide suitable for antigen binding for the MHCclass-1 of the proteasome.

Missense variant gene rs2617170 was detected in KLRC4 in the Turkish and Japanese population. This variation is related to the natural killer (NK) cell gene complex region. This variation was found in 23 of 83 BD patients. It is thought to cause autoinflammation by causing a communication-related pathology between the NK cell and the MHC gene [20]. However, the effect of these variations is still unclear.

The intergenic region between IL23R-IL12RB2 detected in BD is thought to cause increased expression of IL23R. IL23R is expressed in TH17 and macrophages [21].

Intergenetic and intron gene regions have been detected in STAT4-related gene regions. STAT4 causes IL12 and IL23 secretion and Naive T cell to transform into Th1 and Th17 [22].

Genetic studies associated with FUT2 have suggested that it may be associated with disease exacerbation by affecting intestinal bacterial flora in BD [23].

On the other hand, Behcet's Disease has a strong relationship with HLA-B51, and its degree of relationship has been found at different rates in different populations [24]. Some variant genes have also been shown to be associated with BD, albeit weak, at the HLA-A locus [25,26]. Ombrello et al. detected 16 variants of HLA B mature protein amino acid sequence in BD patients by performing HLA Class 1 gene analysis with the Genome wide association studies (GWAS) method. This variation has been shown to cover antigen-binding protein regions in MHC Class-1. It includes the antigen-binding protein region in variations detected at the HLA-A locus. It has been supported that these variations may lead to a pathology in the MHC Class 1 binding site, causing a problem in cytotoxic T cell or natural killer cell (NK) communication and causing inflammation [27]. In another study, the variation in amino acid sequence has shown that the communication between HLA-B and NKIR and KIR3DL1 / KIR3DS1 associated with cytotoxic T cell regulation is affected [28]. Also, ERAP1 affects cytotoxic T cell and NK cell communication with MHC Class1. Gene defects associated with ERAP1 were also detected in Behcet's disease. Recent studies have focused on ERAP1 [29,30]. With all these results, the disease is thought to occur due to defect in MHC Class-1 and NK cell and cytotoxic T cell communication

Conclusion

Gene studies, pathological data, and cytokines related to Behcet's disease pathogenesis show that the disease may have developed due to defects in multiple immune pathways. However, the natural immune system is an important step. With GWAS gene studies, it is thought that more progress will be made on the etiopathogenesis of the disease.

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