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Advances in Pathogenesis of Behcet's Disease and Vogt-Koyanagi-Harada Syndrome

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1. Introduction

Uveitis is one of the leading causes of blindness in the world. It is estimated that uveitis accounts for 10%-15% of the blindness in the western world [1]. More importantly, the blindness caused by uveitis is mostly permanent and irreversible since the retina and optic nerve are damaged by inflammation.

Uveitis was previously defined as inflammation of the uveal tract, which is classically composed of the iris, ciliary body and choroid. Yet in common practice, uveitis refers to inflammation involving any intraocular structure and therefore carries the following names: iritis, iridocyclitis, parsplanitis, posterior uveitis, choroiditis, retinitis and retinal vasculitis. It is usually classified into infectious and noninfectious origins on the basis of predominant etiological characteristics. Behcet's disease (BD) is thought to be an autoinflammatory disease, while Vogt-Koyanagi-Harada (VKH) syndrome is an autoimmune disease. Therefore, we chose BD and VKH, which are two important representative entities among the noninfectious uveitis class, to discuss the recent advances in our knowledge on the pathogenesis of uveitis.

BD is a chronic systemic autoinflammatory disease, characterized by recurrent uveitis, skin lesions, oral and genital mucous ulcers, as well as some complications in central nervous system, gastrointestinal tract and thrombotic events [2]. A high prevalence of BD has been reported along the ancient Silk Road [3], from Asia to the Mediterranean basin countries, such as Turkey, Iraq, Iran, Korea and Japan. The clinical features of BD have been well documented in publications originating from the high incidence countries. Our research group has evaluated the clinical characteristics and associated ocular complications in a large group of

consecutive Chinese BD patients and found that most patients presented a bilateral nongranulomatous anterior, posterior, or panuveitis with a chronic and relapsing course. Uveitis occurred mostly in male patients and in the age group from the second to fifth decade of life. Oral aphthae (100%), skin lesions (78%), and genital ulcers (57.9%) were the typical extraocular findings in patients with BD [4].

VKH syndrome is a well-established immune-mediated multi-organ disorder characterized by a bilateral granulomatous panuveitis frequently associated with extraocular findings including poliosis, vitiligo, alopecia, and central nervous system and auditory signs [5]. It is an autoimmune disease against melanocyte-associated antigens in genetically susceptible individuals. VKH mainly affects certain pigmented races, such as Asians and Native Americans [5-6]. Four clinical stages of uveitis could be developed in patients with VKH syndrome: prodromal, acute, convalescent, and chronic recurrent stages. A clinical analysis based on a large group (n=410) of uveitis patients with VKH syndrome performed by our group showed that the disease was diagnosed most often in young people without a gender predisposition. The intraocular manifestations typically began with choroiditis or chorioretinitis, serous retinal detachment, and optic disc edema, and then proceeded to anterior uveitis if appropriate treatment was not given during the first 2 weeks. Eventually, the eyes developed a recurrent generalized granulomatous uveitis. With regard to the extraocular manifestations, meningismus signs, tinnitus, and abnormal touch sensitivity of the hair frequently occurred before or concurrently with ocular involvement, whereas vitiligo and poliosis usually appear after the uveitis attack [7]. This is possibly due to the autoimmune attack against melanocytes at different sites of the body.

Although the etiology and pathogenesis of BD and VKH syndrome is not completely known, it is hypothesized that abnormalities in the regulation of the immune system and an immunogenetic predisposition are involved in the development of these diseases. Deregulation of Th1, Th17 and regulatory T cells and abnormalities in the associated molecules were found to be involved in the development of these diseases. Recently, two large genome-wide association studies (GWAS) from Japan and Turkey reported an association between single nucleotide polymorphism (SNP) of IL-10, IL-23R/IL-12RB2 gene and BD [8-9]. HLA-DR4 and HLA-DRw53 were reported to be highly associated with VKH syndrome [10], implicating that genetic factors contributed to the pathogenesis of BD and VKH syndrome. The aim of this chapter is to expound the pathogenesis of BD and VKH syndrome with emphasis on new insights in the area of immunoregulation and immunogenetics.

2. Th1 cells and cytokines in Behcet's disease and VKH syndrome

Th1 cells were the first subtype of T help cells that was reported to be involved in the pathogenesis of autoimmune diseases. IFN-γ is the hallmark cytokine of Th1 cells. A number of studies have determined the role of the Th1 cell and its specific cytokine repertoire in the pathogenesis of BD and VKH syndrome. The increased levels of IFN-γ and T-bet, which is

considered as the critical transcriptional factor for Th1 cells, have been observed in the peripheral blood of the patients with active uveitis of BD and VKH syndrome [11-14]. Our study found that S-Ag specific T cells may be involved in the pathogenesis of BD via the production of Th1-dominant cytokines, but not Th17 cytokines [15]. The increased levels of Th1 cell specific cytokines and chemokines in the cerebrospinal fluid (CSF) of VKH patients and in the lesions of active BD patients were also reported [16-17]. El-Asrar et al found an increased levels of IFN-γ in the aqueous humor samples of uveitis from BD, VKH syndrome and HLA-B27-associated uveitis as compared with normal controls; and importantly, the levels of IFN-γ were higher in BD patients than in VKH and HLA-B27-associated uveitis [18], which suggests that IFN-γ may play more important role in the pathogenesis of BD.

In the murine uveitis models, previous reports suggested that Th1 played a pathogenic role during experimental autoimmune uveitis (EAU) development. It was shown that mice neutralized with monoclonal antibodies to IL-12, which drives Th1 differentiation, did not develop EAU [19]. In order to detect whether constitutive ocular expression of IFN-γ influences the course of EAU, Egwuagu et al generated transgenic rats with targeted expression of IFN-γ in the eye and found that IFN-γ markedly accelerated the onset and exacerbated the severity of rat EAU [20]. However, it has been reported that IFN-γ can also provide a protective role in this model. Genetic deletion or neutralization with antibodies against endogenous IFN-γ did not lead to a resistance of EAU induction and development, but rather aggravated the severity of uveitis [21-22]. Mice treated with IL-12 during the first week after immunization appeared to protect the animals from EAU through an IFN-γ-dependent mechanism. It has now been demonstrated that the role of IFN-γ in the development of uveitis is dependent on the stage of disease and the model of EAU that is being studied. IFN-γ confers protection when it is produced during the early stage of the disease. Th1 cells play an essential pathogenic role in the induction of the so called dendritic cell (DC) EAU model, which is induced by the infusion of uveitogenic interphotoreceptor retinoid-binding protein (IRBP) peptide-pulsed DCs. On the other hand, Th17 cells are essential to the induction of classical EAU, which is induced by the immunization with IRBP in the presence of strong adjuvants such as complete Freund's adjuvant and *B. pertusis* [23].

3. Th17 cells and cytokines in Behcet's disease and VKH syndrome

Th17 cells, characterized by their production of IL-17, have been reported be associated with the pathogenesis of many autoimmune diseases, including multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus (SLE). Th17 cells preferentially produce IL-17A, IL-17F, IL-21, and IL-22 [24]. IL-17A, also commonly called IL-17, plays a critical role in the development of allergy and autoimmune responses. IL-17F is mainly involved in mucosal host defense mechanisms, while not required for the induction of experimental autoimmune encephalomyelitis (EAE) and Collagen-induced arthritis (CIA) [25]. As yet no reports have appeared on the role of IL-17F in the pathogenesis of uveitis, thus, whether IL-17F is involved

in human uveitis and EAU needs further investigation. This section aims to review studies regarding Th17 cells and related cytokines in the development of BD and VKH syndrome.

Various studies have shown that Th17 cells contribute to the pathogenesis of BD and VKH syndrome. The previous reports from ours and others have shown that the level of IL-17 by polyclonally stimulated peripheral blood mononuclear cells (PBMCs) and CD4+T cells, and the frequency of IL-17–producing CD4+T cells in PBMCs was higher in patients with active BD or VKH syndrome than the controls [11-12, 26]. Geri et al reported an increase of Th17 cells in peripheral blood and in CSF from active BD patients [27]. Animal studies showed that IL-17 may play a major role in the pathogenesis of EAU. The neutralization of IL-17 by monoclonal antibodies prevented or reversed the intraocular inflammation in the EAU model [28-30]. Adoptive transfer of Th17 cells could induce EAU in the absence of INF-γ [29]. These results indicate that IL-17 plays a proinflammatory and pathogenic role in autoimmune uveitis, and the blockade of IL-17 signaling may represent a therapeutic target in BD and VKH syndrome as well as in other Th17 cell-mediated autoimmune diseases.

IL-21, a member of the IL-2 family of cytokines, can drive Th17 differentiation in an autocrine manner [31-32]. We recently reported a higher level of serum IL-21 and IL-21 mRNA in PBMCs from patients having chronic or recurrent active VKH syndrome as compared with patients having inactive VKH syndrome or healthy controls. Moreover, in vitro experiments showed that IL-21 significantly increased IL-17 production, but had no influence on IFN-γ production by PBMCs or CD4+T cells obtained from either patients or healthy controls [33]. Geri et al observed higher levels of serum IL-21 and IL-21-producing CD4+T cells in BD patients. IL-21 was found to be able to drive Th1 and Th17 differentiation and suppressed the frequency of Treg cells. More importantly, they demonstrated the presence of IL-21-producing T cells in the CSF, choroid plexus, brain parenchyma inflammatory infiltrates and intracerebral blood vessels in active BD with CNS involvement [27]. These results suggest that IL-21 may be involved in the pathogenesis of BD and VKH syndrome and may represent a novel therapeutic target for these diseases. The pathogenic role of IL-21 in autoimmune uveitis is supported by animal models. IL-21R-deficient mice are resistant to EAU, and adoptive transfer of IL-21R-/-T cells reduced the EAU severity. Increased IL-21 in lymph nodes and spleens has been reported during the development of EAU [34-35]. All these findings provide evidence for a role of IL-21 in the pathogenesis of uveitis by promoting Th1 and Th17 cell responses and inhibiting Treg cell development.

IL-22, a member of the IL-10 cytokine family, has recently been reported to be involved in a number of human diseases, including mucosal-associated infections and inflammatory disorders of the intestine, skin and joints. In view of the biological function, controversial effects of IL-22 have been observed in different animal models and human disease. IL-22 seems to play a pathogenic role in experimental arthritis and dermatitis, whereas a protective effect was found in inflammatory bowel disease, experimental hepatitis and collagen-induced arthritis [36-37]. Sugita et al showed that the frequency of IL-22-producing T cell clones from aqueous humor of Behcet's uveitis was higher than that from normal controls. Furthermore,

they demonstrated that CD4^{+}T cells from PBMCs secrete increased amounts of IL-22 in BD patients with active uveitis. Higher IL-22 levels in the supernatants of stimulated PBMCs and CD4^{+}T cells and an increased frequency of IL-22-producing CD4^{+}T cells in BD patients with active uveitis were also reported by our group. In addition, increased IL-22 mRNA expression was found in erythema nodosum (EN) skin lesions, and positively correlated with the presence of EN [38]. The group of Nussenblatt reported an upregulated expression of IL-22 in PBMCs of clinical uveitis patients. IL-22 was shown to damage the physiological integrity of primary fetal retinal epithelium cells and induced their apoptosis [39]. These results suggest that an increased IL-22 may also be involved in the pathogenesis of BD. However, studies in a mouse model of uveitis showed that IL-22 can protect mice from the development of uveitis by inducing the generation of regulatory CD11b^{+}antigen-presenting cells, which were able to convert pathogenic T cells into regulatory T cells [40]. As mentioned, the role of IL-22 in human clinical uveitis and animal models remains controversial and needs further investigation.

4. Molecules modulating Th1 or Th17 cells in Behcet's disease and VKH syndrome

The induction and maintenance of Th1 and Th17 cells requires a large set of molecules. The differentiation of Th17 cells from naïve CD4^{+}T cells is regulated by cytokines [41]. Transforming growth factor-β (TGF-β) and IL-6, broadly expressed by many cell types in the body, including dendritic and epithelial cells, are dominant in the initiation of Th17 cell differentiation [42-45]; IL-23, IL-1β and IL-21, which are products of activated DCs, macrophages, activated T cell or inflamed epithelial cells, possibly expand and maintain the differentiated Th17 cells in the presence of IL-6 and TGF-β1 [31-32, 43, 46-47]. Furthermore, signal transducer and activator of transcription 3 (STAT3) has been found to mediate the initiation of Th17 cell differentiation by these inducing cytokines [48]. IL-12 is an important cytokine responsible for Th1 cell differentiation. IL-27 can induce Tr1 cell differentiation while inhibiting Th17 cell differentiation.

IL-6 has been shown to be a critical mediator of the autoimmune response and inflammation. Various studies have demonstrated that IL-6 was associated with disease activity in BD [49-50]. Studies by Norose et al showed that the level of IL-6 was significantly increased and correlated with the number of lymphocytes in aqueous humor from VKH patients [51]. The infiltrated T cells in the aqueous humor or PBMCs obtained from VKH patients showed an enhanced capability to secrete IL-6 as compared to normal controls [51-52]. Ozdamar et al found that serum levels of IL-6 were higher in BD patients with active uveitis than in those without uveitis [53]. A higher level of IL-6 was also reported in the CSF of patients with active BD with nervous system involvement [54-55]. A case report by Hirano et al showed that tocilizumab, a humanized anti-interleukin 6 receptor antibody, could suppress the clinical manifestations in a patient with refractory BD [56]. Consistent with observations in clinical uveitis, IL-6-deficient mice were not able to generate Th17 cells and were resistant to EAU. Systemic administration of

anti-IL-6 receptor antibody ameliorated EAU by suppressing both systemic and regional Th17 responses [57-58]. Taken together, these findings suggest that IL-6 is involved in the pathogenesis of BD and VKH syndrome, and IL-6 blockade may provide a therapeutic efficacy in treating ocular inflammation in patients with BD or VKH syndrome.

IL-23, which is composed of a unique p19 subunit and a shared p40 subunit of IL-12, is essential in the survival and maintenance of pathogenic Th17 cells. Our earlier studies provided evidence for the involvement of IL-23 in the occurrence of uveitis in BD and VKH syndrome. Active uveitis in both diseases showed a higher level of IL-23 in the serum and supernatants of PBMCs as compared to inactive patients and normal controls [11-12]. IL-23p19 mRNA expression was increased in the EN-like skin lesions from BD patients [59]. Studies by Habibagahi et al showed that the IL-23 expression was strongly associated with the disease activity of uveitis with BD [60]. These results suggest that IL-23 may be a biomarker in the course of BD and VKH syndrome. Animal studies have shown that IL-23 is necessary for the induction of EAU due to its capacity to promote a Th17 effector response. It has been shown that IL-23KO mice are resistant to EAU and specific anti-IL-23 antibody prevented EAU induction [29]. These findings support the hypothesis that the IL-23/IL-17 pathway is involved in the pathogenesis of intraocular inflammation in BD and VKH syndrome.

IL-1β is a key proinflammatory cytokine that promotes Th17 cell differentiation. We recently observed a higher IL-1β production by peptidoglycan (PGN)/lipopolysaccharide (LPS)– induced monocyte-derived macrophages from active ocular BD patients [61]. Pay et al showed a significantly increased level of IL-1β in synovial fluid from BD patients as compared to that from osteoarthritis patients [62]. These results suggest that IL-1β may play a critical role in the pathogenesis of BD. The pathogenic role of IL-1β in uveitis was also proven directly by the observation that IL-1 receptor deficient mice were completely resistant to EAU [63].

IL-12, a heterodimeric cytokine composed of the subunits p40 andp35, is known to induce the differentiation of naïve CD4$^+$T cells into Th1 cells. Studies on the role of IL-12 in clinical uveitis have shown that IL-12 levels in plasma and PBMC culture supernatants were higher in BD with active uveitis [64-65]. Actual measurements of IL-12 in VKH syndrome have not yet been reported. Many studies have shown that Th1 cells are involved in VKH syndrome [13-14], which makes it likely that IL-12 is involved in the pathogenesis.

IL-27, a member of the IL-12 family of cytokines, has been shown to be able to inhibit Th17 cells and that it can induce regulatory Tr1 cells. IL-27 is composed of a unique p28 subunit and a shared EBI3 subunit with IL-35. Our studies on VKH found a decreased IL-27P28 mRNA expression by PBMCs and the lower IL-27 levels in the serum and supernatants of PBMCs in active VKH patients as compared to the inactive patients and normal controls, while the shared EBI3 mRNA expression was not different between the three groups. Furthermore, IL-27 was shown to inhibit the Th17 cell response in a direct manner on CD4$^+$T cells as well as by modulating DCs. Treatment with corticosteroids has been shown to upregulate IL-27 production in vivo and in vitro [66]. An increased levels of IL-27 have been reported in the serum of uveitis patients with BD [67]. Various animal models have been used to examine the role of IL-27 in autoimmune disease and found that the presence of IL-27 could protect mice from

EAE and CIA [68-69]. In the EAU model, an increased expression of IL-27 was observed at the peak of EAU, and further experiments showed that IL-27 could suppress the expansion of Th17 cells in the retina [70]. These observations suggest that an upregulated IL-27 response may contribute to the self-limited inflammation seen in the EAU model. Further clinical studies are needed in clinical uveitis and EAU to obtain further support whether IL-27 may be a potential therapeutic target for BD and VKH syndrome.

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that plays a significant role in the pathogenesis of many inflammatory and autoimmune diseases. It has been reported that the level of TNF-α was increased in the ocular fluids, serum and in the supernatants of stimulated CD4$^+$T cells from active uveitis patients with BD. Furthermore, TNF-α could induce the polarization of Th17 cells in BD patients [71-72]. A similar result was seen in the aqueous humor of VKH patients concerning the expression of TNF-α [18]. In the animal models of EAU it was shown that TNFR1-deficient mice were resistant to EAU through a TNFR1-dependent deficit in macrophage migration to the inflammatory site [73]. Treatment with systemic or local TNF-α inhibition with etanercept in the induction phase of EAU could effectively alleviate the severity of uveitis [74]. The pathogenic role of TNF-α in uveitis was also supported by experiments that showed that TNF-α could disrupt morphologic and functional barrier properties of polarized retinal pigment epithelium cells [75]. Thus, these results also indicate that TNF-α plays an important role in the pathogenesis of uveitis and has provided the basis as a major target for treating inflammatory and autoimmune eye diseases. In clinical trials, a number of reports have shown encouraging results in treating BD and VKH syndrome with anti-TNF-α antibody, such as infliximab [76-77].

A number of other immune-related molecules were also found to be associated with the pathogenesis of BD or VKH syndrome. Our most recent studies have revealed that other proinflammatory mediators, such as osteopontin (OPN), IL-7 and leptin, were also involved in the pathogenesis of BD and/or VKH syndrome. We observed the increased serum levels of OPN, IL-7 and leptin in patients with active BD and/or VKH syndrome, which may promote both Th1 and/or Th17 polarization [78-81]. Consistent with our findings, it has been shown that OPN aggravated the severity of EAU, and blockade of OPN with siRNA prevented the uveitis development [82-83]. IL-7 and leptin have been reported to be involved in the induction and progress of EAE, a model that shares many immunopathogenic mechanisms with EAU [84-85].

Other regulatory molecules may also play a critical role in controlling autoimmunity. 1,25-Dihydroxyvitamin D, miRNA155, IFN-α and IFN-β have all been shown to have an anti-inflammatory role in autoimmune disease. Levels of 1,25-Dihydroxyvitamin D3 and miRNA155 have been shown to be decreased in BD and VKH syndrome. Furthermore, 1,25-Dihydroxyvitamin D3 and miRNA155 were shown to inhibit Th17 cell responses [86-87], supporting its protective role in both BD and VKH syndrome. IFN-α has been effective in treating uveitis in patients with BD and our studies on the possible mechanisms showed that it could inhibit the Th17 cell response and was able to induce the expression of the regulatory cytokine IL-10 [88]. Studies in the animal model of uveitis showed that IFN-β exerted its

inhibitory effect on EAU by inhibiting the Th1 and Th17 cell response [89], suggesting a protective role in uveitis.

5. Treg cells in Behcet's disease and VKH syndrome

Treg cells maintain the immune balance between effector and tolerogenic immune responses. It is well documented that a deficiency in Treg cells can result in the development of autoimmune disease and adoptive transfer of Treg cells effectively prevented and suppressed the severity of inflammation and/or autoimmune disease. Up to now, several subsets of Treg cells have been identified, such as the TGF-β-secreting Th3 regulatory cells [90], $CD8^+CD28^-$T cells [91] and NKT regulatory cells [92]. However, the best characterized subsets of $CD4^+$regulatory T cells are $CD4^+CD25^+FoxP3^+$Tregs and Tr1 cells that secrete IL-10 and lack FoxP3 expression. The important protective role played by these T-regulatory cells in the control of inflammatory and autoimmune disease has generated considerable interest in patients with noninfectious uveitis including BD and VKH syndrome.

$CD4^+CD25^+FoxP3^+$Tregs can be divided into two subpopulations: natural Treg cells (nTreg), which are develop as a distinct lineage of cells in the thymus, and the induced Treg cells (iTreg), which are generated in the periphery from naïve $CD4^+$T cells. They can also be induced in vitro. The difference and relative contributions in immune response of nTreg and iTreg cells are difficult to distinguish. A recent study found that a cell surface molecule neuropilin-1 was expressed on thymus-derived nTreg cells, but not on mucosa-generated $Foxp3^+$iTreg cells [93-94]. This marker can now be used to distinguish the subsets of $CD4^+CD25^+$Tregs. Our studies showed a decreased frequency of $CD4^+CD25^+$Treg cells and $CD4^+CD25^+Foxp3^+$Treg cells in the peripheral blood from active VKH patients. $CD4^+CD25^+$Treg cells from active VKH patients showed a diminished function in suppressing the proliferation of $CD4^+CD25^-$T cells and were less potent in inhibiting the production of IFN-γ and IL-13 by $CD4^+CD25^-$Tcells [95]. These results suggest that a decreased frequency and diminished function of $CD4^+CD25^+$Treg cells are associated with the active uveitis seen in VKH patients. However, Commodaro et al found no significant differences in the frequency of $CD4^+Foxp3^+$and $CD25^+Foxp3^+$T cells as well as no reduction in FOXP3 mRNA expression in mononuclear cells from VKH patients with active or inactive uveitis as compared with healthy controls [96]. The discrepancy may be due to the difference in Tregs subtypes investigated in the two studies (iTreg or nTreg). Patients with BD showed a significantly decreased frequency of Treg cells [27, 97], suggesting that the low level of Treg cells may contribute to the pathogenesis of ocular attacks in BD patients.

Tr1 cells are defined by their high expression of IL-10 and their ability to suppress antigen-specific effector T cell. Unlike $CD4^+CD25^+$Treg cells, which are present from birth, Tr1 cells are inducible cells and can be generated both in vitro and in vivo. It has been reported that IL-27 or CD46 activation in the presence of IL-2 can induce the differentiation of Tr1 cells [98-99]. A defect of CD46-mediated Tr1 cells has been reported in multiple sclerosis [98]. A study by our group revealed a decreased IL-10 production by naïve $CD4^+$T cells under Tr1 cell polarizing conditions in active VKH patients as compared with inactive VKH patients and healthy

controls [66], suggesting that a defect of Tr1 cells might contribute to the pathogenesis of VKH syndrome.

Animal studies showed that Treg cells are involved in the remission of ocular inflammation. nTreg cells and iTreg cells induced by LPS-activated bone marrow dendritic cells inhibited the development of EAU. An increased frequency of $CD4^+CD25^+$Treg cells was associated with the EAU activity, and these Treg cells from EAU mice have a stronger ability to inhibit the proliferation of $CD4^+CD25^-$T cells and decreased IFN-γ production by $CD4^+CD25^-$T cells compared with those obtained from normal control mice. Moreover, transfer of $CD4^+CD25^+$Treg cells obtained from EAU mice on day 14 or 28 inhibited EAU induction [100]. These results suggest that the increased frequency and inhibitory effect of $CD4^+CD25^+$Treg cells in EAU mice may contribute to the monophasic nature and rapid resolution of EAU. Shao and his colleagues found that the suppressive function of Treg cells from animals with recurrent EAU was weaker than those from animals with the monophasic form, indicating that the dysregulation and malfunction of Treg cells in the eye contributed to disease recurrence [101]. Taken together, these results offer an explanation why the uveitis in the BD and VKH syndrome is recurrent while the uveitis in the EAU model is monophasic. The observations demonstrate the important role of $Foxp3^+$Treg cells in maintaining immune tolerance and preventing autoimmunity. Thus, it could be hypothesized that Treg cells in vitro expansion and adoptive transfer back to the patient might be a potential treatment for BD and VKH syndrome.

6. Genetic factors in Behcet's disease and VKH syndrome

The majority of BD is sporadic, but its familial aggregation has been reported [102-103]. BD can be found all over the world, however, its prevalence is particularly high in a peculiar region along the Silk Road extending from the Mediterranean basin to China [2, 104]. BD has been shown to be strongly associated with HLA-B51, which has been confirmed in different ethnic groups [105-106]. Previous studies showed that VKH syndrome is more prevalent in particular ethnic groups, particularly in pigmented groups [7] including Latin-American and Asian populations and displays a familial aggregation pattern [107]. Several HLA genes such as HLA-DR4 and HLA-DRw53, were strongly associated with VKH in a variety of ethnic groups [10, 108-109]. The aforementioned evidence as provided a strong genetic basis for BD and VKH confirmed by familial aggregation, geographical ethnic distribution, and strong association with especially Human leukocyte antigen (*HLA*) antigens. The genes associated with Behcet's disease and VKH syndrome are summarized in Tables 1 and 2, respectively.

6.1. Risk genes in Th1 cell pathway associated with Behcet's disease and VKH syndrome

STAT4, a transcription factor belonging to the Signal Transducer and Activator of Transcription protein family, is required for Th1 development of naive $CD4^+$T cells. Our study has identified an associated locus at STAT4 for BD in a Chinese Han population, and indicated that the risk SNP rs897200 in the STAT4 gene played a pathogenic role through an effect on

STAT4 transcription and IL-17 production [110]. The association of STAT4 with BD was confirmed in a Turkish population [111], suggesting that STAT4 is a common risk gene for BD in different ethnic cohorts.

C-C chemokine receptor type 1 (CCR1) and CCR3 play important roles in the accumulation and activation of inflammatory cells such as the Th1 cell. Recent studies showed that a locus at CCR1/CCR3 was associated with BD in Chinese Han and Turkish populations [111-112]. Functional studies showed a higher expression of CCR1 and migration of monocytes was found in individuals with the risk genotype [111], suggesting that impaired clearance of pathogens may contribute to the development of BD.

IL-18 is a proinflammatory cytokine that stimulates the production of IFN-γ in collaboration with IL-12 by Th1 cells. Studies from Turkish and Korean populations have shown the consistent association with BD in spite of inconsistent result in Korean cohorts [113].

TNF-α has been implicated in the pathogenesis of BD and anti-TNF-α represents an important treatment modality for BD patients [114]. A meta analysis showed an association of TNF-α gene polymorphisms with BD in various ethnic populations [115-117].

6.2. Risk genes in the Th17 cell pathway associated with Behcet's disease and VKH syndrome

Accumulative evidence supports the important role of the IL-23/Th17/IL-17 pathway in mediating chronic inflammatory or immune diseases such as BD and VKH syndrome [11, 95] and suggests the involvement of genes related to this pathway such as IL23R-IL12RB2, JAK1, STAT3, IL-1β, IL-6, IL17 and OPN in BD and VKH syndrome. We investigated the association of IL23R genes with BD in the Chinese Han population [118]. The results showed that two SNPs in IL23R were associated with the susceptibility to BD. Genome-wide association studies also confirmed the association of IL23R-IL12RB2 with BD in Japanese, Turkish and Iranian patients [8-9, 119]. Additionally, we identified the association of STAT3, JAK1, MCP-1 genes with BD in a Chinese Han population [120-122]. Other genes in the Th17 pathway such as IL-6 and IL-1β also showed an association with BD [123-124].

OPN, also known as bone sialoprotein I or early T-lymphocyte activation, may enhance T cell survival and proliferation, and promotes the responses of Th1 and Th17 cells during chronic inflammatory or immune mediated diseases. We examined the OPN serum level in VKH syndrome and the association of OPN polymorphisms and its receptors with this disease [80]. The results showed that the OPN level was significantly increased in the serum of active VKH patients and identified an association of this gene with VKH syndrome in a Chinese Han population. Furthermore, we found the association of JAK1, IL17F with VKH syndrome [125-126]. These studies suggest that genetic variants of cytokines associated to the Th17 pathway may play an important role in the development of BD and VKH syndrome.

6.3. Risk genes in the Treg cell pathway associated with Behcet's disease and VKH syndrome

Mir-146a, one of the miRNAs prevalently expressed in Treg cells, is known as a negative regulator of innate immunity in a variety of immune diseases [127]. We examined the associ-

ation of polymorphisms in mir-146a with BD and VKH syndrome in a Chinese Han population and found that a polymorphism in this gene was associated with BD but not with VKH syndrome [128].

7. Innate immunity in Behcet's disease and VKH syndrome

It has been reported that infection may be involved in the pathogenesis of BD and VKH syndrome. Most of the uveitis patients with BD or VKH syndrome have manifestations of a bacterial or viral infection before the prodromal stage [129-130], suggesting that infectious agents may be a triggering factor to the onset of these diseases. DCs serve as professional antigen-presenting cells and provide the first line of defense against pathologic infections. Toll-like receptors (TLRs) expressed on DCs play a critical role in innate immunity against these pathologic infections. Interaction of DCs with TLR ligands results in the secretion of a number of proinflammatory cytokines that can induce the differentiation of naïve CD4$^+$T cells into different CD4$^+$T cells, including Th1, Th17 and Treg cells. Kirino and his colleagues reported that an increased expression of TLR4 is associated with heme oxygenase-1 reduction in PBMCs from patients with BD, leading to augmented inflammatory responses [131]. The study by Do et al showed a higher level of TLR2 and TLR4 in monocytes from active BD patients [132]. Our recent study showed a higher expression of TLR2, TLR3, TLR4 and TLR8 by either PBMCs, CD4$^+$T cells or monocytes obtained from BD patients as compared with controls. Furthermore, significantly higher levels of IL-1β were produced by monocytes from active BD patients stimulated with known TLR ligands such as LPS and PGN [133]. These results suggest that a higher expression of TLR is associated with ocular Behcet's disease and may partly explain the mechanism by which infection was involved in the pathogenesis. It has been reported that DC deregulation was implicated in the pathogenesis of BD [134]. DCs play a critical role in determining the immune balance between self and non-self and this area is becoming a hotspot for researchers to develop tolerogenic DCs for treating autoimmune disease [135].

8. Summary

With the recent progress in immunology and genetics, environmental triggering factors such as viruses, bacteria or other molecular mimicry are thought to be participated in the outbreak of BD and VKH through interacting with TLRs. The imbalance of pathogenic Th1/Th17 and regulatory T cells and abnormalities in the associated immunoregulatory molecules with the abovementioned T cells are now supposed to be involved in the pathogenesis of these two diseases. The understanding of novel pathogenic mechanisms of both diseases may provide a foundation for developing new strategies to better treat the uveitis.

Genes	Odd Ratio	95% Confidence Interval	Ethnic	References
CCR1/CCR3	0.28	0.2–0.4	Chinese	[112]
CCR5	2.37	1.1- 5.1	Italian	[136]
CD40	1.98	1.38-2.83	Chinese	[137]
CPVL	2.26	1.47–3.45	Turkish	[138]
eNOS	1.88	1.27-2.49	Turkish	[139]
	3.2	1.4-7.3	Korean	[140]
	1.26	2.13-3.62	Tunisian	[141]
ERAP1	4.56	2.88-7.22	Turkish	[111]
FCRL3	0.7	0.5–0.9	Chinese	[142]
ICAM1	1.26	2.13-3.62	Tunisian	[143]
	4.2	1.9-9.3	Italian	[144]
IL1β	3.63	1.23–12.97	Turkish	[123]
IL4	3.40	1.72–7.12	Turkish	[145]
IL6	3.5	1.2-10.0	Korean	[124]
IL10	1.20	1.02-1.40	Iran	[119]
	1.45	1.34-1.58	Turkish, Arab, Greek, UK, Korean, Japanese	[9]
	1.45	1.32–1.60	Japanese, Turkish, Korean	[8]
IL12B	1.8	1.0–3.3	Japanese	[146]
IL18	1.48	1.10–1.97	Turkish	[147]
IL23R-IL12RB2	1.51	1.27–1.78	Iran	[119]
	1.28	1.18-1.39	Turkish	[9]
	1.35	0.95–1.91	Japanese,Turkish, Korean	[8]
	1.86	1.39 -2.49	Chinese	[118]
IRF-1	3.71	1.778-7.770	Korean	[148]
KIAA1529	2.04	1.45–2.88	Turkish	[138]
LOC100129342	1.84	1.32–2.58	Turkish	[138]
m.709G >A	1.40	1.0-1.97	Iranian	[149]
MCP1	1.51	1.05–2.17	Chinese	[122]

Genes	Odd Ratio	95% Confidence Interval	Ethnic	References
MDR1	3.03	1.41-6.54	Turkish	[150]
MIF	1.46	1.19–1.79	Chinese	[151]
miR-146a	1.33	1.17-1.52	Chinese	[128]
MMP2	0.6	0.44-0.87	Korean	[152]
MMP9	0.371	0.152-0.905	Korean	[153]
MTHFR	1.70	1.23–2.35	Turkish	[154]
NRAMP1	1.88	1.21-2.93	Turkish	[155]
PDGFRL	0.59	0.49–0.72	Chinese	[156]
Protein Z	6.8	2.6-17.9	Turkish	[157]
PTPN22	2.4	1.2 to 4.7	UK, Middle East	[158]
SLC11A1	0.60	0.37-0.95	Korean	[159]
STAT3	1.712	1.238–2.369	Chinese	[121]
STAT4	1.45	1.3-1.6	Chinese	[110, 160]
	1.27	1.17–1.37	Turkish	[111]
SUMO4	23.40	2.33-235.54	Korean	[161]
	1.41	1.01-1.97	Tunisian	[162]
	1.7	1.3–2.2	Chinese	[106]
TGFBR3	0.617	0.441-0.863	Chinese	[163]
TLR4	1.96	1.26-3.26	Korean	[164]
	1.67	1.08-2.60	Japanese	[165]
TNF-α	1.68	1.10-2.56	Moroccan	[116]
	3.08	1.73-5.47	Iranian Azeri Turk	[117]
TNFAIP3	2.03	1.65-2.49	Chinese	[166]
TREM-1	2.723	1.285-5.770	Korean	[167]
UBAC2	1.5	1.2-1.7	Chinese	[168]
UBASH3B	1.71	1.23–2.38	Turkish	[138]
VDR	1.89	1.32-2.71	Tunisians	[169]
VEGF	0.10	0.011-0.875	Korean	[170]

Table 1. Summary of the associated genes with Behcet's disease

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