

Review

HSV-Induced Systemic Inflammation as an Animal Model for Behçet's Disease and Therapeutic Applications

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Abstract: Behçet's disease (BD) affects multiple organs. It is mainly characterized by recurrent oral, skin, and genital aphthous ulcers, and eye involvement. Successful management of BD is increasing, although its etiology remains unclear. A number of etiologies have been proposed, including environmental, genetic, viral, and immunological factors. To understand its complex etiology and improve its management, animal models of BD have been used to enable more effective therapeutic applications with increased clinical significance. An herpes simplex virus (HSV) type 1-induced BD mouse model has shown disease characteristics similar to those seen in BD patients. An HSV-induced BD animal model has been used to test various therapeutic modalities. The applied modalities are several materials that are derived from natural products, conventional therapeutics, and possible biologics. In this review, we provided how they regulate inflammation in an HSV-induced BD model.

Keywords: Behçet's disease; herpes simplex virus; animal model; application

1. Introduction

Behçet's disease (BD) is a chronic, relapsing, multi-systemic, and vascular inflammatory disorder that affects many organ systems, including mucocutaneous, ocular, vascular, arthritic, gastrointestinal, and central nervous systems [1]. Until now, the pathogenesis is not conclusive. Several factors, including environmental pollutants, infections, genetic polymorphism, and immune dysregulation, have been suggested as factors affecting the pathogenesis of BD. It seems likely all these factors may contribute together [2]. Herpes simplex virus (HSV) infection [3–6] is believed to be a triggering factor of BD. HSV-induced BD animal models have been shown to have similar inflammatory responses compared with BD patients, such as mucocutaneous, ocular, vascular, arthritic, and gastrointestinal involvement [7]. Recent progress in the treatment of BD is getting better, but more needs to be done. Using HSV-induced inflammatory BD animal models, therapeutic effects of natural products, and new biological agents have been applied in recent years. They are reviewed and discussed here.

2. Etiopathogenesis of Behçet's Disease

2.1. Clinical Significance of HSV

In 1937, Hulusi Behçet proposed that the syndrome might be caused by viral infection, in his first description of BD. However, he could not demonstrate that the virus was HSV in his publication. In 1953, Sezer et al. [5] isolated the virus from ocular fluid of patients. 211-bp HSV-1 DNA fragments and serum anti-HSV-1 antibodies were found in patients with BD [6]. Later, Lee et al. [8] detected HSV

DNA in the saliva of patients with BD, and hypothesized that HSV infection might be the trigger of BD. Tojo et al. also detected HSV genome in the skin lesions of BD patients [9], and Eglin et al. found HSV-1 genome by using an in situ DNA–RNA hybridization method in the peripheral blood mononuclear cells of BD patients [3]. Based on these results, Sohn et al. [7] developed an animal model of BD by inoculating 1×10^6 p.f.u. HSV type 1 (KOS strain) to needle-scratched earlobes of Institute of Cancer Research (ICR) mice, which are commonly used as an outbred population [10], and found that the mice developed BD-like symptoms, including genital ulcers, oral ulcers, skin lesions, eye lesions, arthritis, and intestinal ulcers [7]. These induced BD-like symptoms were similar to the clinical manifestations of BD in patients. Even though this mouse model was developed by inoculation with HSV, the disease pattern was very similar to that of human BD when evaluated in immune modulation experiments. HSV ribonucleotide reductase 1 mRNA was not detected in skin lesions of mice through polymerase chain reaction (PCR), even this lesion was induced by HSV inoculation [1]. This means the symptoms are not derived from HSV infection itself, but from dysregulated or uncontrolled immune responses triggered by HSV. HSV type 1 UL48 proteins were highly reactive to the serum of BD patients and BD mice [11]. In addition, in human herpesvirus 4, EBV (Epstein-Barr virus) shedding was increased in BD patients [12]. Innate and adaptive immune responses, including Th1 and Th2 imbalance, are thought to be responsible for managing HSV evading, and for maintaining surveillance during latency [13]. The pathogenic role of HSV related to immune dysregulation in BD is important, so it needs to be further clarified [14]. Many scientists developed animal models, including the HSV-induced model, for use in Behçet’s disease. They are listed in Table 1.

Table 1. Published animal models of Behçet’s disease (1979–2018).

Models and Symptoms	Published Number of Papers
Environmental pollutants→Mucocutaneous lesions in miniature swine	1
Human 60 kD heat shock protein-derived peptide 336–351→Uveitis in rats	1
HLA-B51 Transgenic mice→Excessive function of peripheral blood neutrophils but no symptoms	1
Herpes simplex virus type 1→Oral, genital, and skin ulcers, eye involvement, arthritis, and intestinal involvement in ICR mice and C57BL/6 mice	26
Tropomyosin→Inflammation in the skin, joints, and eyes of Lewis rats	2
Retinal soluble antigen (S-Ag)→Uveitis in rats	1
Sera from seven NeuroBD patients→Reduced locomotor activity in rats	1

2.2. Genetic Susceptibility

Genetic susceptibility of BD has been widely studied. It is well-known that human leukocyte antigen (HLA)-B gene, particularly HLA-B51, is associated with BD patients [15]. However, the relative risk of BD associated with HLA-B51 varies widely among different ethnic populations. HLA-B51 allele is more frequent in some populations where BD is virtually unknown [16]. It has been recognized that the association of HLA-B51 with BD is stronger in Turkish and Japanese populations than in the Western population. Transgenic mice with HLA-B51 generated by Takeno et al. [17] have shown neutrophil hyperfunction without showing any clinical manifestations that mimic BD. This indicates the HLA-B51 molecule alone is insufficient to induce clinical BD. This result suggests that other factors are involved in BD susceptibility.

HLA-G gene variants have also been studied in BD [18,19]. HLA-G was first identified in placenta. It is involved in maintaining tolerance of maternal immune system to semi-allogeneic fetus [20–22]. HLA-G has an inhibitory effect on cytotoxicity of natural killer (NK) and T-cells, and T-cell proliferation [23]. HLA-G can inhibit trans-endothelial migration of NK cells [24], shift the cytokine balance toward Th2 dominance [25], and suppress the proliferation of allogeneic CD4+ T lymphocytes [26,27]. These results suggest that HLA-G has specific inhibitory effects on immune cells. Qa-2 is the functional homolog of HLA-G in mice [28]. HSV-induced BD mice show decreased Qa-2 levels. Down-regulation of Qa-2 is known to bring the deterioration of BD-like symptoms [29].

2.3. Immunological Dysregulation

HSV induced BD-like symptoms have been reported in mice [7]. However, virus infection alone is insufficient to explain the pathogenesis of BD. In BD patients, dysregulations of immune functions have been reported. There is plenty of evidence for aberrant T-cell responses in BD. Type 1 helper T cells (Th1) are known to secrete interleukin (IL)-2, and interferon gamma (IFN γ) activates macrophages, and elicits delayed hypersensitivity reactions, while type 2 helper T cells (Th2) can produce IL-4, IL-5, and IL-10 to suppress cell-mediated immunity. In BD, these cytokines perform a cross-regulatory function between Th1 and Th2 subsets. Th1/Th2 imbalance is thought to be an important factor in BD [30,31]. The induction of macrophages promotes Th1-dependent cellular immune responses and suppresses Th2 cell activity [32]. Sohn et al. [33] have demonstrated that deletion of macrophages decreases the incidence of BD in mice. Deletion of macrophages also up-regulates Th2 cytokines that are closely related to improvement of BD symptoms. Regulatory T (Treg) cells play an important role in the pathogenesis of autoimmune disorders, including BD. Frequencies of Treg cells are reduced in the peripheral blood of BD patients with eye lesions [34]. Therefore, low levels of CD4+CD25+ regulatory T cells can be a factor in the pathogenesis of BD. According to Shim et al. [35], when CD4+CD25+ T cells isolated from healthy mice are transferred to BD mice, the disease severity is significantly down-regulated by Treg cells transferred in a dose-dependent manner. Increased Treg cells up-regulated IL-10 and TGF- β levels, but down-regulated IFN γ , tumor necrosis factor alpha (TNF α), IL-6, and IL-17 levels.

3. Therapeutic Applications of Inflammatory Mice Model of Behçet's Disease Induced by HSV

3.1. Natural Products

3.1.1. TNF α Inhibition with Derivatives of *Gentiana Macrophylla Radix*

TNF α is a potent paracrine and endocrine mediator of inflammatory and immune functions. There is growing evidence showing that TNF α plays an important role in the management of inflammatory diseases, including BD. In BD patients, TNF α production is high [36]. Infliximab (anti-TNF α antibody) and Etanercept (soluble TNF receptor) have been used to treat BD patients [37,38]. Inhibition of TNF α expression by administration of TNF α small interfering RNA (siRNA) can ameliorate HSV-induced BD mice. The severity score of BD was significantly decreased compared to that in the control group [39]. SK126 and SK94 are synthesized pyridine derivatives based on gentianine, a major component of *Gentiana Macrophylla Radix*. When SK126 and SK94 were used to treat TNF α -stimulated human umbilical vein endothelial cells, they down-regulated adhesion molecules such as ICAM-1, VCAM-1, and E-selectin [40]. In addition, oral administration of SK126 and SK94 effectively down-regulated serum levels of TNF α in HSV-induced BD mice accompanied by symptom improvement [40] (Figure 1).



Figure 1. Changes in symptoms of herpes simplex virus (HSV)-induced Behçet's disease mouse after treatment with SK126.

3.1.2. Herba Taraxaci

Herba Taraxaci (*Taraxacum mongolicum* Hand.-Mazz.) is frequently used for bacterial and viral infections. It has anti-inflammatory, anti-carcinogenic, anti-allergic, anti-hyperglycemic, and analgesic activities [41]. Its known effects include reducing heat, decreasing edema, and clearing toxic substances in inflamed areas. In addition, it has antibiotic effects against *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae* [42]. Herba Taraxaci contains taraxasterol, choline, inulin, and pectin [43]. Treatment of BD mice with Herba Taraxaci can induce IL-4 and improve symptoms. Herba Taraxaci can alter Th1/Th2 balance by increasing IL-4 and Th2 immune responses [33,43]. In addition, Herba Taraxaci can induce Fas-mediated apoptosis of abnormal proliferating leukocytes involved in the induction of BD symptoms [43]. Nakamura et al. have suggested that activated CD4+ T cells may cause severe chronic inflammation due to the insufficient expression of Fas in BD patients [44]. A combination therapy of Herba Taraxaci and colchicine can reduce symptoms in 80% of BD mice, much higher than colchicine (30%) or famciclovir (40%) treatment alone. Herba Taraxaci alone or in combination with colchicine can up-regulate frequencies of IL-10 secreting splenocytes. Increased IL-10 by Herba Taraxaci might have acted as an improvement factor. Thus, combination therapy with natural products can be another strategy for BD treatment.

3.1.3. Chitosan

Chitosan is a biocompatible, biodegradable, and nontoxic natural polymer with high cationic potential [45]. Chitosan is a safe and effective adjuvant with many biological effects on drug delivery [46]. A mixture of chitosan and pCIN-mIL-4 DNA vector can significantly increase IL-4 mRNA and IL-4 protein levels after in vivo mouse administration [47]. Oral administration of pCIN-mIL-4 DNA vector in combination with chitosan has effectively delivered DNA vector to intestinal tissues of mice. Our recent study has shown that chitosan itself can be a potential immune modulator [48]. Oral administration of chitosan significantly up-regulated frequencies of DX5+ natural killer cell populations in peripheral blood leukocytes (PBL). In HSV-infected mice, chitosan increased the frequencies of CD4+ T cells, CD8+ T cells, and CD11c+ dendritic cells in PBL. In addition, chitosan treatment down-regulated the levels of anti-HSV antibodies in the serum of HSV-infected mice, compared to the control group [48]. Thus, chitosan can be used as an adjuvant for gene delivery and an immune modulator by oral administration.

3.2. DNA Vector

3.2.1. Interleukin-4

Macrophages are phenotypically heterogeneous. They perform various activities in parallel with adaptive immune responses of Th1 and Th2. M1 macrophages are activated in response to endogenous or exogenous inflammatory stimuli such as Th1 cytokine IFN γ [49] while M2 macrophages are activated by Th2 cytokines such as IL-4 or IL-13 [50]. During the chronic stage of infection, macrophages are further activated by cytokines secreted by T cells. Increased IL-4 may induce the apoptosis of IFN γ -producing macrophages [51]. According to the counter-regulation model of Th1 and Th2 cytokines, an increase of IL-4 might decrease IFN γ producing macrophages in BD mice, or induce apoptosis of IFN γ -secreting macrophages [51,52]. Treatment of recombinant IL-4 can significantly reduce the M1/M2 ratio in mice, and alleviate BD symptoms by downregulating IL-17 and IL-8 [53]. Subcutaneous injection of the IL-4-expressing vector by gene gun bombardment also improves BD symptoms in mice by enhancing serum IL-4, which alters the Th1 response toward the Th2 response [51]. Increase of mRNA and protein levels of IL-4 were also observed after the administration of a mixture of chitosan and pCIN-mIL-4 in mice [47].

3.2.2. C-C Chemokine Ligand 21

Chemokine ligand 21 (CCL21) is a C-C chemokine family produced in the reticular cells of secondary lymphoid organs. CCL21 binds to its receptor CCR7. The level of CCL21 is lower in the synovial fluid of BD patients. It has been suggested that a lack of CCL21 is associated with inflammation [54,55]. HSV-1-induced BD symptomatic mice have also shown a lower expression of CCL21 compared to asymptomatic mice. Transfection of pcDNA3.1-CCL21 DNA vector can increase CCL21 protein expression in RAW 264.7 cells (macrophage like, Abelson leukemia virus transformed cell line) while intraperitoneal injection of pcDNA3.1-CCL21 can increase the frequencies of CCR7+ PBL in normal mice and BD mice [56]. Expression of CCL21 is also associated with the up-regulation of CD8+CD44+ memory T cells and CD8+CD62L-memory T cells. In BD patients, the frequencies of CD4+CD45RO+ memory T cells are increased after symptom improvement [57,58]. Therefore, the use of CCL21 can help improve BD by regulating CCR7+ cells and memory T cells.

3.3. RNA and siRNA

3.3.1. Polyinosinic:Polycytidylic Acid (Poly I:C)

Polyinosinic:polycytidylic acid (Poly I:C) is a mismatched double-stranded RNA. One strand is a polymer of inosinic acid, while the other strand is a polymer of cytidylic acid. Poly I:C induces IL-15 and IL-15 receptor alpha (IL-15R α) and stimulates the production of memory T cells [59–61]. Poly I:C administration can increase IL-15R α in normal mice and HSV-induced BD mice, leading to ameliorated BD symptoms [62]. Our previous study has confirmed that CD8+CD44+ and CD8+CD62L- memory T cells are significantly lower in BD mice. Poly I:C application can significantly increase CD4+CD44+ memory T cells and CD8+ central memory T cells in BD mice. It has been reported that the long-term survival of CD8+ memory T cells is correlated with an improvement in BD symptoms [56,62,63]. Poly I:C may affect the long-term survival of memory T cells. It can increase the frequencies of memory T cells. In addition, Poly I:C can up-regulate IL-10, a potent anti-inflammatory cytokine, in BD mice. Increase of IL-10 level has been found to be accompanied by lower IL-23R mRNA and IL-17A protein levels [62]. Taken together, these findings suggest that Poly I:C might have therapeutic application in BD treatment.

3.3.2. TNF α siRNA

TNF α is an effective paracrine and endocrine inflammatory mediator. It can transmit signals between the immune system and other cells [39,64]. In several acute and chronic inflammatory diseases such as inflammatory bowel disease [65], Crohn's disease [64], Rheumatoid arthritis [66], atopic dermatitis [67], and Behçet's disease [36], overexpression of TNF α has been observed. It has been published anti-TNF α antibody therapy can improve BD symptoms [68,69]. siRNA intraperitoneal treatment can reduce the overexpression of TNF α in the serum of BD mouse. siRNA binds RNA-Induced Silencing Complex (RISC), a multiprotein component complex in cytoplasm, and then the passenger strand of siRNA departs, thereby commencing the RNA interference process via target mRNA cleavage, and degradation results [70]. Such decrease in the level of TNF α can improve HSV-induced BD symptoms in mice [39]. Infliximab is now widely used in the management of autoimmune diseases including BD. Infliximab blocks the action of TNF α by binding to it and preventing TNF α from binding to signaling receptors on the cell surface. TNF α siRNA can act faster than infliximab. Thus, it is more effective than infliximab in BD mice [39]. TNF α siRNA has shown therapeutic efficacy in HSV-induced BD mice, supporting that RNAi therapeutics or gene silencing can be a potential new class of drug for managing inflammatory diseases, including BD.

3.3.3. Interleukin-6 siRNA

IL-6 is a multifunctional cytokine secreted by lymphoid and non-lymphoid cells. It is involved in the regulation of immune responses and inflammation [71,72]. HSV type 1 and type 2 are

potent inducers for IL-6. IL-6 is released at a relatively early stage following HSV infection [73,74]. IL-6 levels are significantly higher in BD patients and HSV-induced BD mice, indicating that IL-6 plays a pathogenic role in BD [75,76]. It has been reported that treatment with IL-6 siRNA can reduce serum IL-6 levels and decrease expression of ROR γ t (retinoic acid-receptor-related orphan nuclear receptor gamma t), and TNF α in mice [75]. IL-6 siRNA treatment can also increase Treg cells and improve BD symptoms, such as oral ulcers, scrotal inflammation, arthritis, and skin ulcers (Figure 2) [35,75]. IL-6 siRNA treatment can also reduce IL-17 and IL-23p40 (alpha-receptor subunit of IL-23 and IL-12) levels in the sera of BD mice [75]. Therefore, IL-6 siRNA can be used as a therapeutic to decrease IL-6 levels in BD patients.



Figure 2. IL-6 small interfering RNA (siRNA) improves HSV-induced Behçet's disease symptoms. IL-6 siRNA (1.5 μ g in 200 μ L of 5% glucose solution) was intraperitoneally injected twice at 3-day intervals.

3.3.4. miRNA-21 Antagomir

MicroRNAs (miRNAs) are small non-coding RNAs that play critical roles in immune functions [77]. Single miRNA also has a substantial impact on immune regulation. Decreased miRNA-155 levels are associated with ocular BD patients [78]. miRNA-146a gene polymorphisms have also been found in ocular BD patients [79]. miRNA-21 is frequently up-regulated in solid tumors [80]. Overexpression of miRNA-21 in cancer promotes cell survival and reduces apoptosis. miRNA-21 is one of the most abundant miRNAs in T cells, especially in effector T cells. Its expression is dynamically changed during T cell differentiation [81,82]. miRNA-21 is highly expressed in BD patients and HSV-induced BD mice [83]. Intraperitoneal treatment of miRNA-21 antagomirs targeting the host miRNA-21, can improve BD symptoms in mice with the downregulation of IL-17, IL-6, and TLR-4 [83]. Choi et al. [83] have clearly shown that miRNA-21 expression is correlated with BD symptoms in both patients and mice (Figure 3).



Figure 3. miRNA-21 inhibition with miRNA-21 antagomir improves HSV induced Behçet's disease symptom.

3.4. Protein Complex

3.4.1. IL-2/IL-2 Antibody Complex

Serum levels of IL-2 in BD patients are controversial. Some studies have reported that IL-2 serum levels are significantly higher in BD patients, with frequencies of IL-2 producing CD4 $^{+}$ and CD8 $^{+}$

cells being higher in active BD patients than those in inactive BD patients [71,84]. On the other hand, other studies have shown that IL-2 levels are not significantly different between BD patients and healthy controls, although soluble interleukin 2 receptor (sIL-2R) is elevated in active BD patients, suggesting that sIL-2R is related to disease activity [85]. IL-2R is composed of alpha (CD25), beta (CD122), and gamma (CD132) subunits. It has been reported that IL-2R β levels are significantly lower in BD patients, and HSV induced BD mice [86]. Treatment with IL-2/S4B6-1 (IL-2/anti-mIL-2 antibody complex) can significantly upregulate IL-2R α , IL-2R β , IL-2R γ , and regulatory T cells. IL-2/S4B6-1 also regulates NK cell maturation in normal mice and HSV-induced BD mice [86]. Elevated IL-2R β is associated with increased proportions of central memory T cells. Up-regulation of central memory T cells is correlated with inhibition of BD deterioration in mice [56,87]. Likewise, IL-2R β blocking with anti-IL-2R β antibody injection exacerbates BD symptoms with down-regulated frequencies of IL-2R β + cells in mice [86]. Choi et al. [86] have shown a correlation between IL-2R subunit expressing cells and BD in both patients and mice.

3.4.2. IL-15/IL-15R α Complex

IL-15 is a pleiotropic cytokine involved in the pathogenesis of diverse inflammatory diseases, including BD. IL-15 is highly expressed in the serum, cerebral fluids, and ocular fluids of BD patients, whereas IL-15R α expressing cells are lower in the peripheral blood of BD patients [88]. IL-15R α restricts aberrant immune stimulation and decreases the risk of uncontrolled IL-15 exposure [89]. Recently, it has been shown that an IL-15/IL-15R α complex expressing the vector or the recombinant mIL-15/IL-15R α -Fc protein complex can decrease disease severity and ameliorate symptoms in HSV-induced BD mice [90]. According to a previous report, frequencies of Treg cells are down-regulated in BD mice [35]. rmIL-15/IL-15R α -Fc treatment can increase the frequencies of Treg cells that can attenuate BD symptoms [90]. In addition, treatment with anti-TNF α antibody, infliximab, can increase IL-15R α + cell frequencies. Therefore, IL-15/IL-15R α complex can be used as a therapeutic candidate for BD.

3.5. Vitamin & Galactose Derivatives

3.5.1. Vitamin D3

TLR-2 and TLR-4 are expressed in mouse and human macrophages and monocytes. Accumulated TLR-2 and TLR-4 expressing cells have been found in lesions of BD patients [91]. TLR-2 expressing cells play a pivotal role in initiating destructive Th1-type responses at the site of BD lesions [92]. This suggests that the regulation of TLR-2 and TLR-4 might be involved in BD pathogenesis. Vitamin D reduction is associated with increased renal inflammation and BD. Vitamin D3 treatment can reduce chemokine synthesis and monocyte trafficking, and downregulate TLR-2 and TLR-4 on mononuclear cells [93–95]. Treatment with vitamin D3 (1,25(OH) $_2$ D $_3$) can also down-regulate TLR-2 and TLR-4 in the peritoneal macrophages of BD mice in a dose-dependent manner, leading to reduced severity scores [96]. Serum levels of IL-6 and TNF α are also down-regulated after treatment with 1,25(OH) $_2$ D $_3$ in BD mice [96]. These results suggest that 1,25(OH) $_2$ D $_3$ can be used as a complementary treatment for BD.

3.5.2. N-Acetylgalactosamine (GalNAc), a Mannose Receptor Ligand

CD206 is a mannose receptor that is mainly expressed on macrophages. It is involved in various autoimmune diseases. Frequencies of CD206 positive cells are higher in whole leukocytes and monocytes of active BD patients than in those of inactive BD patients. This indicates that CD206 is involved in the pathogenesis of BD [97]. CD206 can bind to HSV-1 through macrophage and dendritic cells. HSV-2 infected patients show enhanced prevalence of CD206 expressing dendritic cells [98]. CD206 has elevated frequencies in HSV-1 induced BD mice [99]. Colchicine and pentoxifylline are commercial drugs used for BD patients. They can decrease frequencies of CD206 in HSV-1-induced BD

mice, accompanied by down-regulation of IL-17. Treatment with 4-sulfated N-acetyl galactosamine (GalNAc), a ligand of CD206, can significantly decrease CD206 in BD mice. It can also reduce the levels of IL-17 [99]. These results suggest that the inhibition of CD206 may provide therapeutic benefits for BD patients.

4. Conclusions

Although several immunological abnormalities have been demonstrated, the precise mechanism of inflammatory changes in BD has not yet been completely determined. Up to date, HSV-induced BD mouse models have been consistently used (Tables 1 and 2) as they produce symptoms that are most similar to those seen in patients with BD. Further research is needed to find the most appropriate therapy to overcome this rare, intractable disease. Based on results obtained from BD mice induced by HSV, successful treatment strategies for BD are expected to be developed in the near future. In addition, HSV inoculation alone is not sufficient to develop BD models. HSV inoculation to HLA B51 transgenic mice [17] may increase BD-like phenotypes and can be a potent animal model for BD. Erp1 (Endoplasmic reticulum aminopeptidase 1) is also a candidate gene for BD [100]. HSV inoculation to Erp1 deficient mice also can be a more advanced animal model for BD. Management of BD is still unsatisfactory because of its complex entities (Figure 4). Further study in advanced animal models will be significant progress for the BD research field.

Table 2. Applied therapeutic modalities for HSV-induced Behçet’s disease mice.

Categories	Applied Materials	Therapy Targets
Conventional therapies	Thalidomide	↓TNF α
	Infliximab	↓TNF α
	Etanercept	↓TNF α
Natural products	Derivatives of <i>Gentiana macrophylla</i> Radix	↓TNF α
	<i>Taraxacum mongolicum</i> Hand.-Mazz.	↑IL-10
	Chitosan	↑IL-4
Potential therapies	IL-4	↑IL-4
	C-C chemokine ligand 21	↑CCR7
	Poly I:C	↑IL-15R α , IL-10
	TNF α siRNA	↓TNF α
	IL-6 siRNA	↓IL-6
	miRNA-21 antagomir	↓miRNA-21
	IL-2/IL-2 Ab complex,	↑IL-2R α ,
	IL-15/IL-15R-Fc complex	↑IL-15R α
	Vitamin D3	↓TLR-2, ↓TLR-4,
4-sulfated N-acetyl galactosamine	↓CD206	

Note: IL, Interleukin; ↓, Downregulation; ↑, Upregulation.

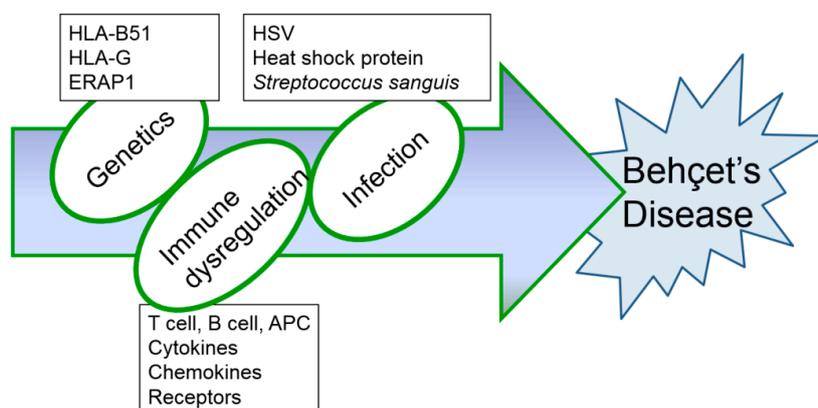


Figure 4. Hypothesized etiopathogenetic scheme of Behçet’s disease.

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