Pathogenesis and Emerging Therapeutic Lines in Behcet's Disease: Integrating Genetic, Vascular, and Immunologic Insights with Clinical Translation

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Abstract

Background: Behcet's disease (BD) is a chronic, relapsing, multisystem vasculitis characterized by recurrent mucocutaneous, ocular, vascular, and neurological involvement. Its pathogenesis is complex and multifactorial, involving a combination of genetic susceptibility, environmental and microbial triggers, vascular-endothelial dysfunction, and dysregulation of both innate and adaptive immune responses. While considerable progress has been made in delineating these mechanisms, the integration of these diverse pathogenic pathways into a cohesive model remains incomplete, creating a gap between molecular understanding and clinical application. This review synthesizes current evidence on the pathogenesis of BD, emphasizing mechanisms of interest to rheumatologists, and explores how these insights can inform emerging targeted therapies. Genetic studies have highlighted associations with HLA-B51 and other non-HLA loci, implicating antigen presentation, immune regulation, and endothelial homeostasis. Epigenetic changes, including DNA methylation and microRNA dysregulation, further suggest a dynamic gene–environment interface. Infectious and microbiome-related triggers may initiate or perpetuate immune activation in genetically predisposed individuals, potentially through molecular mimicry or alteration of mucosal immunity. Endothelial dysfunction, driven by oxidative stress, pro-inflammatory cytokines, and neutrophil hyperactivity, is central to the vascular phenotype of BD, contributing to thrombotic and aneurysmal complications. Dysregulation of innate immunity—particularly neutrophil activation, inflammasome signaling, and aberrant monocyte/macrophage responses—intersects with adaptive immune abnormalities, including skewed T helper 1/ T helper 17 responses, reduced regulatory T cell function, and chronic antigenic stimulation. Emerging therapies targeting interleukin (IL)-1, IL-6, IL-17, and tumor necrosis factor (TNF) -α, along with small molecules modulating Janus kinase (JAK) signaling, offer promising avenues for precision medicine in BD. The integration of vascular biology, immunology, and genetic insights into therapeutic decision-making could shift clinical management toward personalized strategies, minimizing irreversible organ damage. This review aims to provide rheumatologists and clinician-scientists with an updated, integrative overview of BD pathogenesis, bridging molecular and clinical perspectives. By linking pathogenic mechanisms to novel therapeutic opportunities, we underscore the importance of multidisciplinary and translational approaches in addressing the unmet needs of patients with BD.

Keywords: *Pathogenesis, Emerging Therapeutic, Immunologic Insights.*

Introduction

Behcet's disease (BD) is a chronic, relapsing, inflammatory disorder classified among variable vessel vasculitides, affecting arteries and veins of all sizes. First described by Hulusi Behçet in 1937 as a triad of oral aphthous ulcers, genital ulcers, and uveitis, it is now recognized as a multisystem condition with protean manifestations including vascular, neurological, gastrointestinal, and dermatological involvement. The disease predominantly affects populations along the ancient Silk Road, with the highest prevalence reported in Turkey, Middle Eastern countries, and parts of East Asia, but it is increasingly diagnosed worldwide due to migration and heightened clinical awareness [1]. The burden of BD is significant, with ocular involvement leading to blindness in up to 20% of cases, vascular lesions predisposing to life-threatening events, and recurrent mucocutaneous flares impairing quality of life [2].

Despite decades of research, the pathogenesis of BD remains incompletely understood. A strong genetic association with HLA-B51 is well established, but its pathogenic role is not fully elucidated. Non-HLA genetic loci, environmental and microbial triggers, and immune dysregulation converge on vascular inflammation and tissue damage, yet the interplay between these elements is complex and variable among patients [3]. The vascular pathology in BD is distinctive, characterized by a predilection for venous thrombosis and aneurysm formation without the atherosclerotic changes seen in other vasculitides. This vascular-centric nature makes BD particularly relevant to rheumatologists, who must integrate systemic inflammatory control with prevention of vascular complications [4].

The last decade has seen rapid advances in our understanding of both innate and adaptive immune pathways in BD, including the role of neutrophil hyperactivity, inflammasome signaling, and T helper 17 (Th17) - mediated inflammation. Concurrently, new therapeutic approaches have emerged, targeting specific cytokines and intracellular signaling pathways. However, translating pathogenic insights into clinical practice remains challenging due to disease heterogeneity, lack of specific biomarkers, and limited high-quality randomized controlled trials [5].

This review aims to provide an integrative analysis of BD pathogenesis, encompassing genetic, vascular, immunologic, and environmental dimensions, while linking these mechanisms to emerging therapeutic strategies. By consolidating current evidence into a cohesive model, we seek to bridge the gap between molecular research and bedside management, offering rheumatologists a comprehensive framework for both understanding and treating BD [6].

Genetic and Epigenetic Factors

Genetic predisposition plays a central role in the pathogenesis of Behcet's disease (BD), with the strongest and most consistently replicated association found with the human leukocyte antigen (HLA) allele HLA-B51. Meta-analyses have confirmed that HLA-B51 carriage increases the risk of BD approximately 5- to 6-fold, with higher odds ratios in endemic regions such as Turkey, Iran, and Japan [7]. Although the precise pathogenic mechanism remains unclear, hypotheses include altered peptide binding and presentation, modulation of natural killer (NK) cell activity, and effects on endoplasmic reticulum aminopeptidases that influence antigen processing [8]. Importantly, not all HLA-B51 carriers develop BD, underscoring the need for additional genetic and environmental triggers in disease expression [9].

Beyond HLA-B51, genome-wide association studies (GWAS) have identified several non-HLA loci linked to BD susceptibility. Variants in genes such as ERAP1 (endoplasmic reticulum aminopeptidase 1), IL10 (interleukin-10), and IL-23 receptor–IL-12 receptor Beta 2 (IL23R–IL12RB2) have been implicated, suggesting that antigen processing, cytokine signaling, and regulation of the IL-23/Th17 axis are critical in BD pathogenesis [10]. The ERAP1–HLA-B51 interaction appears epistatic, with certain ERAP1 haplotypes influencing disease risk only in HLA-B51–positive individuals [11]. Additionally, polymorphisms in chemokine receptor 1(CCR1), signal transducer and activator of transcription 4 (STAT4), and killer cell lectin-like receptor subfamily C member4(KLRC4) highlight the importance of leukocyte trafficking, signal transduction, and NK cell function in pathogenesis of BD [12].

Epigenetic modifications add another dimension to genetic susceptibility, providing a potential link between environmental exposures and immune dysregulation in BD. DNA methylation studies have revealed that

hypomethylation of pro-inflammatory genes such as IL-6 and TNF-α in peripheral blood mononuclear cells of BD patients was correlated with disease activity [13]. Histone modification patterns, although less extensively studied, suggest enhanced chromatin accessibility in inflammatory loci. MicroRNAs (miRNAs) such as miR-155 and miR-146a, known regulators of immune homeostasis, are dysregulated in BD and may contribute to sustained inflammation by modulating cytokine production and neutrophil activation [14].

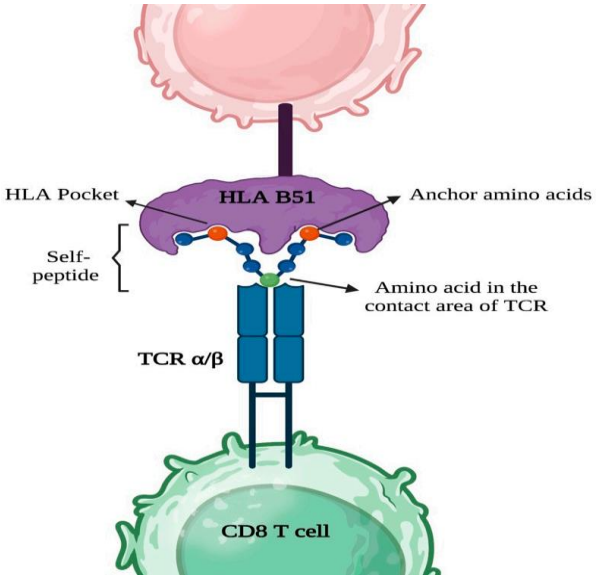

Figure 1: It illustrates the process of HLA class I presentation of peptides to the T cell receptor of CD8+ T cells. Anchor amino acids play a definitive role in peptide binding to HLA class I molecules. While T cell receptors exhibit poly specificity, the specific contact residues on the peptide are very important for their recognition [12].

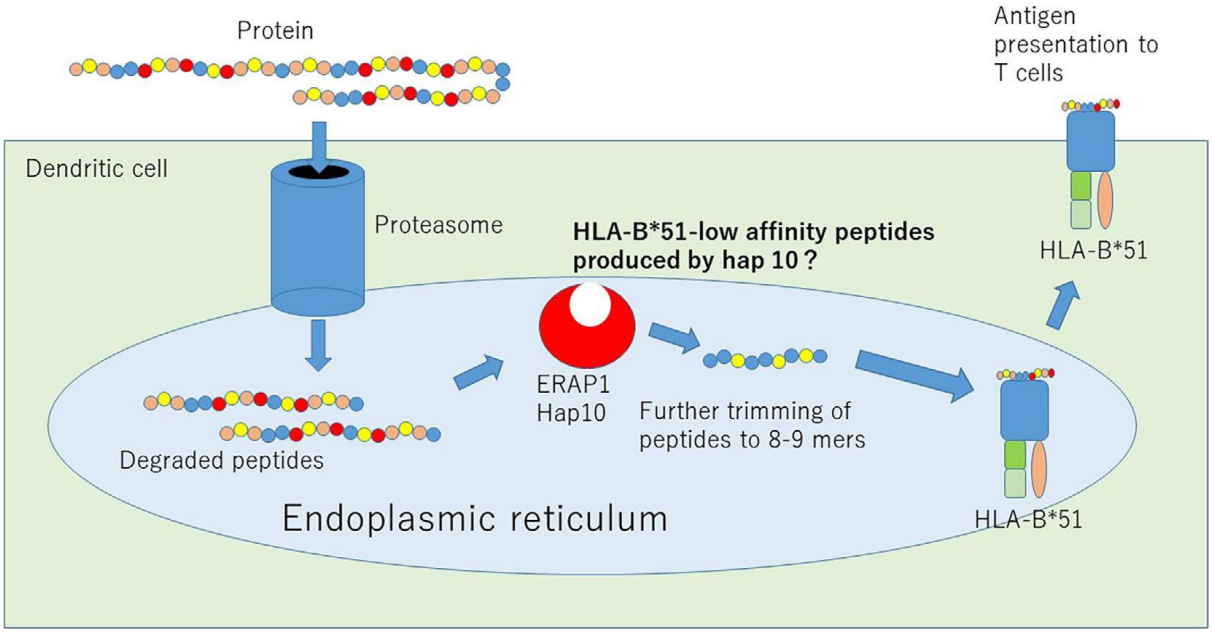

Figure 2: It describes ERAP1-mediated antigen processing in BD [13].

The interplay between genetic variants, epigenetic changes, and environmental triggers likely determines not only susceptibility but also disease phenotype. For example, certain HLA-B51 subtypes and ERAP1 variants have been associated with ocular-predominant disease, while IL10 polymorphisms may influence mucocutaneous versus vascular presentations [15]. Understanding these genotype–phenotype relationships

could enable stratified risk prediction and inform targeted prevention strategies in high-risk populations. [7–15]

Environmental and Microbial Triggers

While genetic susceptibility sets the stage for Behçet's disease (BD), environmental and microbial factors are believed to initiate or exacerbate disease in predisposed individuals. Infectious agents have long been suspected as potential triggers, supported by epidemiologic patterns and immunologic observations. Among these, *Streptococcus sanguinis*—a common oral commensal—has garnered particular interest. Elevated serum antibodies against streptococcal heat-shock protein (HSP)-65 and cross-reactivity with human HSP-60 suggest a role for molecular mimicry in triggering autoreactive immune responses [16]. Similarly, certain viral agents, including herpes simplex virus type 1 (HSV-1), have been implicated through the detection of viral DNA in mucocutaneous lesions and enhanced inflammatory responses to HSV antigens in BD patients [17].

Geographic clustering of BD along the ancient Silk Road has led to hypotheses involving regional microbial exposures and dietary habits. Gut microbiome studies have revealed reduced microbial diversity in BD patients, particularly a depletion of butyrate-producing bacteria such as *Roseburia* and *Faecalibacterium prausnitzii*, along with an overrepresentation of taxa like *Escherichia coli* [18]. Dysbiosis may compromise intestinal barrier integrity, enhance mucosal immune activation, and influence systemic inflammation through altered short-chain fatty acid metabolism [19].

Environmental factors beyond infectious exposures also appear relevant. Smoking has been variably reported as a risk factor, potentially through its effects on vascular endothelium and oxidative stress, though some studies suggest a paradoxical protective effect on certain mucocutaneous manifestations [20]. Seasonal variations in disease flares, with higher activity in spring and autumn in some cohorts, raise the possibility of environmental allergens or climatic factors influencing immune reactivity [21].

Importantly, the interaction between environment and host genetics shapes the immune landscape of BD. For example, HLA-B51 carriers may mount exaggerated inflammatory responses to specific microbial peptides, while certain ERAP1 haplotypes may modulate peptide trimming from environmental antigens, affecting T cell activation thresholds [22]. These insights underscore the multifactorial nature of BD pathogenesis, where genetic background dictates susceptibility, but environmental triggers determine the timing, severity, and phenotype of disease expression.

Vascular and Endothelial Dysfunction

Vascular involvement is a defining pathological feature of Behçet's disease (BD) and is unique among vasculitides in its capacity to affect arteries and veins of all calibers. Unlike atherosclerotic vascular disease, BD-related vasculopathy is driven primarily by inflammatory injury to the endothelium, resulting in a pro-thrombotic and aneurysm-prone state. Histopathological studies reveal perivascular and transmural infiltration by neutrophils and lymphocytes, with endothelial cell swelling, fibrinoid necrosis, and elastic lamina disruption [23]. Venous thrombosis is particularly common, occurring in up to 40% of patients with vascular BD, while arterial disease often presents as aneurysm formation, most notably in the pulmonary arteries, which carries a high risk of rupture and mortality [24].

Endothelial dysfunction in BD is multifactorial, involving direct inflammatory injury, oxidative stress, and immune-mediated cytotoxicity. Circulating endothelial cells and endothelial microparticles are elevated in BD, correlating with disease activity and vascular involvement [25]. Functional studies using flow-mediated dilation techniques demonstrate impaired endothelial-dependent vasodilation, reflecting reduced nitric oxide bioavailability and increased oxidative stress. Elevated levels of endothelin-1, a potent vasoconstrictor and pro-inflammatory mediator, further contribute to vascular tone dysregulation and inflammatory recruitment [26].

Neutrophil hyperactivity plays a pivotal role in vascular pathology. Activated neutrophils in BD produce excessive reactive oxygen species (ROS) and form neutrophil extracellular traps (NETs), which not only damage the endothelium but also provide a scaffold for thrombus formation. Increased NET burden has been demonstrated in both active and quiescent BD, suggesting a persistent pro-thrombotic milieu [27]. In

parallel, platelet activation and elevated thrombin generation further amplify the coagulation cascade, creating a state of thrombophilia that is inflammatory rather than purely mechanical in nature [28].

The vascular pathology of BD challenges conventional thromboembolic management strategies. Anticoagulation alone may be insufficient or even hazardous in the presence of arterial aneurysms, where immunosuppressive control of inflammation is paramount. This underscores the importance of early recognition of endothelial injury and aggressive anti-inflammatory therapy to prevent irreversible vascular damage. Linking vascular biology to BD's immune and genetic features is essential for developing targeted interventions that address both inflammation and thrombosis without exacerbating bleeding risk [29].

Innate Immune Dysregulation

Innate immunity is a central driver of inflammation in Behçet's disease (BD), with neutrophils playing a particularly prominent role. Neutrophils from BD patients exhibit exaggerated chemotaxis, phagocytosis, and oxidative burst activity, even during clinically quiescent periods. This hyperresponsiveness is linked to increased production of reactive oxygen species (ROS) and the formation of neutrophil extracellular traps (NETs), which not only damage surrounding tissue but also promote a pro-thrombotic environment by serving as a scaffold for fibrin deposition [30]. The persistence of these activated neutrophil signatures supports the hypothesis that BD is characterized by a chronically "primed" innate immune system [31].

Monocytes and macrophages are also dysregulated in BD, contributing to both vascular injury and systemic inflammation. These cells display heightened expression of Toll-like receptor (TLR)s, particularly TLR2 and TLR4, leading to amplified responses to microbial and endogenous danger-associated molecular patterns (DAMPs) [32]. This hyperactivation promotes secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6, which not only perpetuate innate immune responses but also shape downstream adaptive immunity [33].

The inflammasome pathway, particularly the NLRP3 inflammasome, has emerged as a key molecular mediator linking innate immune activation to cytokine release in BD. Enhanced NLRP3 expression and caspase-1 activation have been demonstrated in BD monocytes, resulting in elevated IL-1β and IL-18 production [34]. These cytokines amplify neutrophil recruitment and contribute to mucocutaneous, ocular, and vascular lesions. Importantly, the inflammasome's role provides a mechanistic rationale for the efficacy of IL-1 blockade in some refractory BD cases [35].

Natural killer (NK) cells, though less studied, exhibit altered cytotoxic function and cytokine production in BD. Reduced NK cell-mediated cytotoxicity, coupled with a skewed pro-inflammatory cytokine profile, may impair the regulation of autoreactive T cells and sustain chronic inflammation. Collectively, these innate immune abnormalities create a feed-forward loop in which exaggerated microbial and inflammatory sensing leads to persistent vascular and tissue damage, setting the stage for maladaptive adaptive immune responses [36].

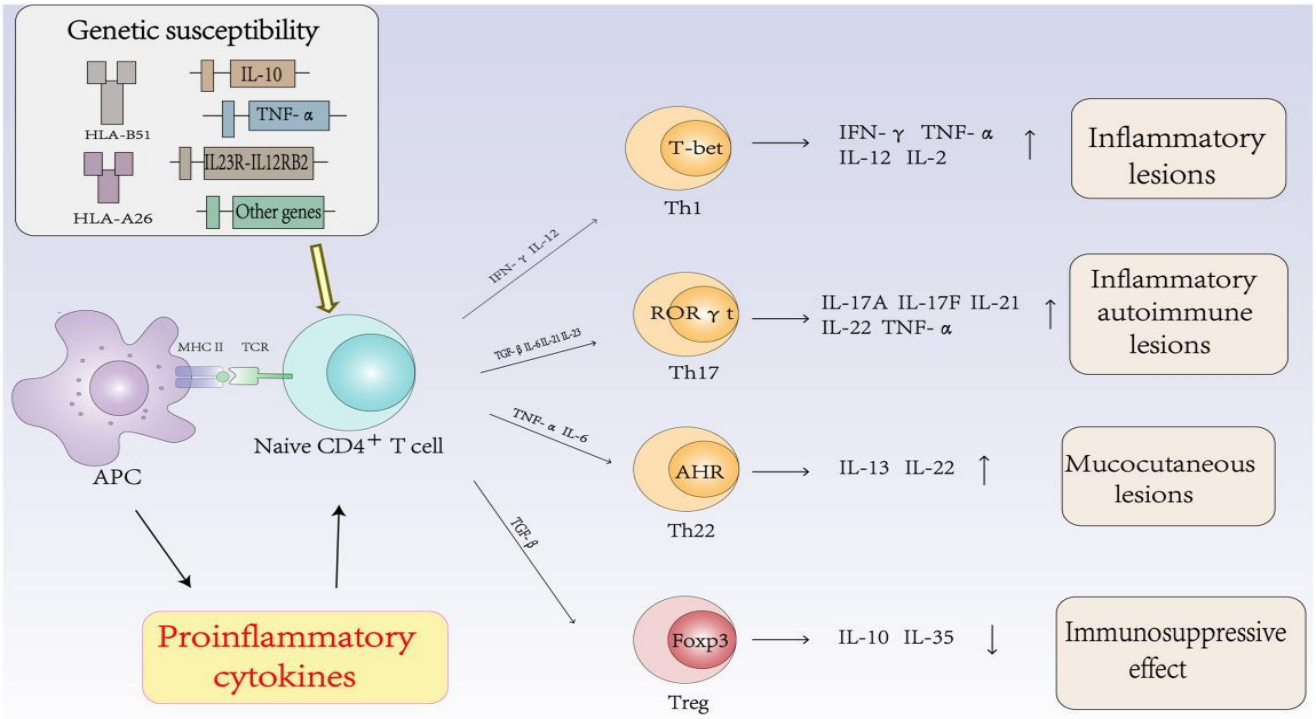

Figure 4 : It illustrates the role of T cell subtypes and their cytokines in the pathogenesis of behcet's disease [36].

Adaptive Immune Dysregulation

Adaptive immunity in Behçet's disease (BD) is characterized by an imbalance between pro-inflammatory effector T cell subsets and regulatory mechanisms. A hallmark feature is the predominance of T helper 1 (Th1) and T helper 17 (Th17) responses. Increased frequencies of Th1 cells producing interferon-gamma (IFN-γ) have been documented in both peripheral blood and affected tissues, particularly in patients with active ocular and vascular disease [37]. Parallel expansion of Th17 cells, which secrete interleukin-17A (IL-17A) and IL-22, further drives neutrophil recruitment, endothelial activation, and tissue inflammation [38]. The Th1 and Th17 axes appear to be mutually reinforced, with IL-23 and IL-12 cytokine pathways serving as critical upstream regulators [39].

Regulatory T cells (Tregs), which normally maintain immune tolerance, are numerically and functionally impaired in BD. Studies have shown reduced Treg frequencies and diminished suppressive capacity, correlating with higher disease activity scores [40]. This loss of regulation may permit persistent activation of autoreactive T cells and exacerbate chronic inflammation. Additionally, an imbalance between Tregs and Th17 cells has been proposed as a predictor of disease severity, suggesting that restoration of this ratio could be a therapeutic goal [41].

B cells and humoral immunity also contribute to BD pathogenesis, though their role is less well defined. Elevated levels of circulating plasma blasts and increased production of autoantibodies against endothelial cells have been reported, particularly in vascular BD [42]. These antibodies may directly damage endothelial cells or amplify inflammation via complement activation and Fc receptor engagement. Moreover, B cells can act as antigen-presenting cells, promoting Th1 and Th17 differentiation and sustaining the inflammatory cascade [43].

Chronic antigenic stimulation—potentially from persistent microbial antigens or self-antigens released during tissue injury—may maintain adaptive immune activation in BD. This ongoing stimulation fosters a cycle in which effector T and B cells perpetuate inflammation, recruit innate immune cells, and drive vascular pathology. These insights into adaptive immunity not only enhance understanding of disease mechanisms but also point to potential therapeutic strategies targeting IL-17, IL-23, and co-stimulatory pathways [44].

Neuroinflammation and CNS Involvement

Neurological involvement in Behçet's disease (BD), often termed neuro-Behçet's disease (NBD), occurs in approximately 5–10% of patients and represents one of the most disabling manifestations. NBD can be broadly classified into parenchymal and non-parenchymal forms, with the former involving inflammatory lesions of the brain and brainstem, and the latter typically related to cerebral venous sinus thrombosis secondary to vascular involvement [45]. Parenchymal NBD is pathologically characterized by perivascular infiltration of neutrophils, lymphocytes, and macrophages, leading to small vessel vasculitis and subsequent tissue necrosis [46]. Lesions are often localized to the brainstem, basal ganglia, and diencephalon, consistent with the clinical presentation of pyramidal signs, cranial neuropathies, and neuropsychiatric symptoms [47].

The pathogenesis of NBD integrates both vascular and immune-mediated mechanisms. Endothelial dysfunction and blood–brain barrier (BBB) disruption allow the entry of activated immune cells and inflammatory mediators into the central nervous system (CNS). Upregulation of adhesion molecules such as Intercellular Adhesion Molecule (ICAM-1) and Vascular Cell Adhesion Molecule 1 (VCAM-1) on cerebral endothelial cells facilitates leukocyte trafficking, while increased levels of matrix metalloproteinases contribute to BBB breakdown [48]. Within the CNS, Th1 and Th17 cells, along with activated microglia, produce pro-inflammatory cytokines including IL-6, TNF-α, and IFN-γ, which amplify neuroinflammation and neuronal injury [49].

Innate immune pathways, particularly neutrophil activation and inflammasome signaling, also play a role in NBD. Neutrophil extracellular traps (NETs) have been detected in cerebrospinal fluid (CSF) during acute attacks, suggesting their contribution to both vascular occlusion and parenchymal damage [50]. Elevated CSF levels of IL-1β and IL-18 further implicate inflammasome activity, providing a mechanistic link to systemic BD pathogenesis [51].

The interplay between systemic inflammation and localized CNS immune responses may explain the relapsing-remitting course of NBD. Moreover, the overlap between CNS and vascular pathology in BD emphasizes the need for integrated pathophysiological models that consider the CNS as both a target and amplifier of systemic disease processes. Understanding these mechanisms not only guides immunosuppressive strategies but also informs neuroprotective approaches aimed at preserving cognitive and functional outcomes [52].

Integrative Pathogenesis Model

The pathogenesis of Behçet's disease (BD) is best understood as the result of a dynamic interplay between genetic predisposition, environmental triggers, vascular biology, and immune dysregulation. In genetically susceptible individuals—most notably those carrying HLA-B51 and specific non-HLA risk alleles—environmental factors such as microbial antigens or dysbiosis initiate aberrant immune responses. These triggers activate the innate immune system, particularly hyperresponsive neutrophils and monocytes, leading to excessive production of reactive oxygen species (ROS), neutrophil extracellular traps (NETs), and pro-inflammatory cytokines including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α) [53].

This exaggerated innate activation primes and sustains adaptive immune responses, skewing T helper cell populations toward Th1 and Th17 phenotypes while impairing regulatory T cell (Treg) function. The resulting cytokine milieu, enriched in interferon-gamma (IFN-γ), IL-17, and IL-23, perpetuates inflammation and recruits additional neutrophils to sites of vascular and tissue injury [54]. Meanwhile, activated B cells produce autoantibodies against endothelial components, potentially exacerbating vascular injury via complement activation and Fc receptor-mediated cytotoxicity [55].

Central to BD's clinical manifestations is vascular and endothelial dysfunction. Endothelial cells, damaged by both direct immune attack and oxidative stress, exhibit reduced nitric oxide availability, increased expression of adhesion molecules, and release of pro-thrombotic factors. This culminates in a distinctive vasculopathy characterized by thrombosis and aneurysm formation rather than the atheromatous changes seen in other systemic vasculitides. The persistent inflammatory-thrombotic loop is fueled by NETs, platelet activation, and coagulation cascade amplification [56].

Organ-specific manifestations reflect variations in vascular anatomy, immune microenvironments, and local tissue susceptibility. For example, mucocutaneous lesions arise from small-vessel immune complex deposition and neutrophilic infiltration in superficial dermal and mucosal vessels, whereas pulmonary artery aneurysms result from destructive transmural vasculitis of large arteries. Neuro-Behçet's disease represents the intersection of systemic vasculitis with central nervous system (CNS) inflammation, facilitated by blood–brain barrier disruption [57].

By conceptualizing BD as a network disorder—where genetic, microbial, vascular, and immune nodes are interconnected—clinicians and researchers can better identify therapeutic targets. This model also explains the heterogeneous clinical spectrum, as variability in any one pathway (e.g., microbial exposure, HLA subtype, Th17 predominance) can shift disease phenotype and severity. Such an integrated view is essential for developing precision medicine strategies tailored to the patient's dominant pathogenic drivers [58].

Therapeutic Implications and Emerging Targets

Advances in the understanding of Behçet's disease (BD) pathogenesis have directly influenced therapeutic strategies, shifting from broad immunosuppression toward targeted modulation of specific inflammatory pathways. Traditional mainstays such as corticosteroids, azathioprine, and cyclophosphamide remain essential for acute disease control, particularly in severe ocular, vascular, and neurological involvement, but their nonspecific immunosuppressive effects carry significant long-term toxicity [59]. The recognition of TNF-α as a central cytokine in BD inflammation has led to the widespread adoption of anti-TNF agents such as infliximab and adalimumab, which have shown efficacy in refractory ocular, vascular, and neurological disease, often inducing rapid remission [60].

Targeting the IL-1 pathway has emerged as a promising approach, particularly in patients with prominent innate immune activation and elevated inflammasome activity. Anakinra, canakinumab, and gevokizumab have demonstrated benefit in small case series and trials, reducing mucocutaneous lesions, arthritis, and ocular flares [61]. Similarly, blockade of the IL-6 receptor with tocilizumab has shown efficacy in refractory uveitis and vascular involvement, likely by dampening both innate and adaptive immune responses [62].

Given the prominent Th17/IL-23 axis in BD pathogenesis, agents such as secukinumab (anti-IL-17A) and ustekinumab (anti-IL-12/23) have been explored, with mixed but encouraging results in mucocutaneous and articular disease [63]. Janus kinase (JAK) inhibitors, including tofacitinib and baricitinib, offer an oral small-molecule approach capable of modulating multiple cytokine pathways simultaneously, and early reports suggest efficacy in refractory vascular and neurological BD [64].

Beyond direct cytokine blockade, therapeutic strategies targeting vascular biology are of growing interest. Statins, with their pleiotropic anti-inflammatory and endothelial-protective effects, have been proposed as adjuncts in vascular BD, though robust trial data are lacking [65]. Antiplatelet and anticoagulant therapies remain controversial; while anticoagulation may address thrombotic risk, it does not correct the underlying inflammatory vasculopathy and may be hazardous in aneurysmal disease, emphasizing the need for individualized risk–benefit assessment [66].

The integration of genotype–phenotype correlations into treatment selection represents a future frontier. For instance, patients with HLA-B51 and ERAP1 variants may preferentially benefit from IL-1 blockade, while those with dominant Th17 signatures could respond better to IL-17 or IL-23 inhibitors. Such precision medicine approaches, coupled with validated biomarkers for disease activity and relapse risk, could transform BD management from empiricism to targeted intervention [67].

Conclusion and Future Perspectives

Behçet's disease (BD) exemplifies the complexity of systemic inflammatory disorders, with pathogenesis arising from an intricate convergence of genetic predisposition, environmental triggers, vascular pathology, and immune dysregulation. Over the past two decades, advances in genomics, immunology, and vascular biology have provided a more coherent picture of the disease process, revealing distinct yet interconnected pathways that drive clinical manifestations. Rheumatologists are now better equipped to interpret BD through an integrated lens—recognizing that neutrophil hyperactivation, Th1/Th17 skewing, impaired regulatory mechanisms, and endothelial dysfunction are not isolated phenomena but components of a unified inflammatory-thrombotic network [68].

Therapeutic evolution has mirrored these insights. The shift from nonspecific immunosuppression toward cytokine-targeted and pathway-specific interventions reflects a broader trend toward precision medicine in rheumatology. Agents targeting TNF-α, IL-1, IL-6, and IL-17 have expanded the therapeutic approaches of BD, offering improved disease control in refractory cases and sparking renewed optimism for organ preservation. However, disease heterogeneity, the absence of robust biomarkers, and variable treatment responses underscore the need for individualized care strategies. Personalized medicine approaches, informed by genotype–phenotype associations and immunologic profiling, represent a promising yet underdeveloped avenue for optimizing patient outcomes.

Future research should prioritize multicenter, randomized controlled trials to validate emerging therapies across diverse clinical phenotypes and ethnic backgrounds. Biomarker discovery—spanning molecular, imaging, and functional domains—is critical for early diagnosis, flare prediction, and monitoring therapeutic efficacy. Further exploration of the gut–immune–vascular axis, epigenetic regulation, and microbiome modulation may open novel preventive and therapeutic possibilities. In parallel, longitudinal studies are needed to clarify the long-term safety and durability of biologic and small-molecule therapies in BD.

Ultimately, bridging the gap between molecular insight and clinical translation will require sustained collaboration between rheumatologists, immunologists, vascular specialists, neurologists, and basic scientists. By embracing an integrative, multidisciplinary approach, the field can move closer to the goal of precise, effective, and safe disease control minimizing irreversible organ damage while enhancing quality of life for patients living with BD.

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