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The roles of immune cells in Behçet's disease

Dan Hu[1] and Jian-Long Guan[1*]

Abstract
Behçet's disease (BD) is a systemic vasculitis that can affect multiple systems, including the skin, mucous membranes, joints, eyes, gastrointestinal and nervous. However, the pathogenesis of BD remains unclear, and it is believed that immune-inflammatory reactions play a crucial role in its development. Immune cells are a critical component of this process and contribute to the onset and progression of BD. By regulating the function of these immune cells, effective control over the occurrence and development of BD can be achieved, particularly with regards to monocyte activation and aggregation, macrophage differentiation and polarization, as well as T cell subset differentiation. This review provides a brief overview of immune cells and their role in regulating BD progression, which may serve as a theoretical foundation for preventing and treating this disease.

Keywords Behçet's disease, Immune cells, Macrophages, Monocytes, Neutrophils, NK cells, T cells

Introduction

Behçet's disease (BD) is a chronic inflammatory disorder of unknown etiology that can affect the skin, mucous membranes, joints, eyes, nervous and gastrointestinal tract [1]. The incidence of BD varies globally, and while its pathogenesis remains incompletely defined, the immune-inflammatory mechanism is widely considered to be the primary driver [2]. Innate immunity and adaptive immune activation are recognized as crucial mechanisms in the pathogenesis of BD [3]. The activation of both the innate and adaptive immune systems by various cytokines plays a crucial role in the pathogenesis and progression of BD patients [4]. Immunological aberrations plays a predominant role in the pathogenesis of BD [5]. Innate immune cells comprise monocytes, macrophages, natural killer (NK) cells, and neutrophils among others, while adaptive immune cells consist of T lymphocytes and B lymphocytes [6]. These cells participate in the pathogenesis of Behçet's disease (BD) through various differentiation phenotypes and cytokine secretion. The aggregation of T lymphocytes, macrophages, neutrophils, and other immune cells with high expression levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) is observed in BD. This review summarizes recent research progress on the role of immune cells in BD and considers their potential as therapeutic targets.

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Elucidation of immune cells function

Monocytes in BD

According to the surface expression of CD14 and CD16 (FcγRIII), monocytes can be divided into three subsets: classical monocytes ($CD14^{+}CD16^{-}$), intermediate monocytes ($CD14^{+}CD16^{dim}$) and non-classical monocytes ($CD14^{dim}CD16^{high}$) [7]. Classical monocytes have the ability to differentiate into macrophages and play a crucial role in initiating inflammatory responses, while non-classical monocytes are responsible for maintaining vascular homeostasis and exerting anti-inflammatory effects [8]. Gazzito et al. have observed a reduction in total and classical monocyte counts, while intermediate monocyte subsets increased in patients with BD

compared to healthy controls (HC) [9]. This was further corroborated by Li et al.'s study, which posited that the proportion of non-classical monocytes in BD decreased and exhibited a correlation with disease activity. Classical monocytes in patients with BD can stimulate TNF-a production and facilitate Th1 differentiation. The levels of IL-6 and phosphorylated p65 (p-p65) were elevated in both classical monocytes and intermediate monocytes [10]. In addition, analysis of monocyte heterogeneity revealed the accumulation of C1q-high ($C1q^{hi}$) monocytes in peripheral blood mononuclear cells (PBMCs) of patients with BD. These $C1q^{hi}$ mononuclear cells exhibited enhanced phagocytic activity and secretion of pro-inflammatory cytokines (IL-6 and TNF-α) [11]. Monocytes from patients with Behcet's disease exhibit heightened production of pro-inflammatory cytokines, as well as increased expression of CD14 and staining with 25F9 and G16/1 antibodies. Additionally, levels of soluble CD14 (sCD14) monocyte activation markers are elevated in the serum of these patients. These cytokines significantly enhance adhesion between normal neutrophils and endothelial cell monolayers [12]. The increased chemotaxis of neutrophils is believed to play an important role in the pathogenesis of BD, and plasma soluble factors can increase the chemotaxis of neutrophils [13]. Neves et al. pointed out that compared with HC, TLR2 was highly expressed in BD monocytes, and serum sCD14 concentration was positively correlated with CD14 expression in peripheral blood monocytes and BD Current Activity Form (BDCAF) score. Monocytes may produce neutrophil-stimulated proinflammatory factors through TLR2 that play a role in BD [14].

The lymphocyte-to-monocyte ratio (LMR), a crucial inflammatory marker, has demonstrated its ability to predict the onset, progression, and survival of certain autoimmune diseases [15, 16]. In patients with BD, LMR is significantly reduced in their blood and serves as a statistically significant predictor for BD [17]. High-density lipoprotein cholesterol (HDL-C) possesses anti-inflammatory and anti-oxidative properties that provide protection for endothelial cells [18]. The monocyte to HDL-C ratio (MHR) serves as an inflammatory biomarker for various diseases. A significant correlation exists between MHR value and clinical severity of BD, rendering it a potential indicator for evaluating BD disease activity [19]. Moreover, MHR can reflect endothelial dysfunction and systemic inflammation in patients with BD [20].

Vascular endothelial growth factor (VEGF) is an endothelium-specific mitogen that stimulates angiogenesis in response to ischemia and hypoxia, while also inducing increased vascular permeability [21]. Monocyte Chemokine Protein-1 (MCP-1), also known as chemokine ligand 2 (CCL2), is primarily expressed by inflammatory cells and endothelial cells, promoting monocyte migration [22]. VEGF and MCP-1 levels were significantly elevated in BD patients with thrombosis, thereby promoting the aggregation and adhesion of monocytes [23]. The increase in platelet-monocyte complexes was significant among BD patients with large vascular involvement, which may be associated with thrombotic events in BD [24].

Fc gamma receptors (FC-γRs) are a family of receptors in the Fc part of IgG, expressed on the surface of hematopoietic cells. The human FC-γRs three types of members, FC-γRI, FC-γRII, and FC-γRIII, all of which mediate phagocytosis [20]. FcγRIIb is the only inhibitory Fc receptor that plays a role in controlling immune and inflammatory responses [25]. FcγRIII serves as a surface marker for non-classical monocytes. Research has revealed that the expression of FcγRIIb is reduced while that of FcγRIII is elevated in BD patients' monocytes, and this phenomenon correlates with indicators associated with BD activity, such as erythrocyte sedimentation rate and C-reactive protein. This may result in overactivation of BD monocytes, thereby exacerbating the disease [26].

CXCL10 is a chemokine belonging to the ELR (-) CXC subfamily, characterized by the presence of the (C-X-C motif). It can be secreted by various cell types including endothelial cells, Th1 type cells, effector CD8+T cells and innate lymphocytes such as NK cells upon induction by interferon (IFN)-γ [27]. CXCL10 protein was found to be upregulated in CD14+blood monocytes of patients with BD upon IFN-γ stimulation. Dysregulation of CXCL10 mRNA at the post-transcriptional level may contribute to the characteristic inflammatory response observed in BD [28]. P2×7 receptor (P2×7r), a member of a family of receptors stimulated by extracellular adenosine triphosphate (ATP) stimulates, is mainly expressed in monocytes and is an effective mediator for promoting the processing and release of pro-inflammatory cytokines [29]. The expression of P2×7r was significantly elevated in monocytes from patients with BD compared to HC. Activation of P2×7r significantly increased the release of IL-1β from lipopolysaccharide-stimulated BD monocytes, and TNF-α can upregulate the expression and function of P2×7r in monocytes [30]. BD exhibits an excessive inflammatory response to monosodium urate crystals. Uric acid (UA) can significantly enhance the activity levels of NO, IL-1β, and caspase-1 in peripheral blood monocytes of BD patients, thereby exacerbating the development of BD [31]. These studies indicate that the transitional activation of monocytes has emerged as a distinctive feature of BD, contributing significantly to its pathogenesis.

Macrophages in BD

Macrophages, which originate from monocytes and play a pivotal role in phagocytosis and digestion, exhibit

elevated TLR2/4 expression as well as increased production of IL-1β and ROS in monocyte-derived macrophages from patients with active BD. The activation of ROS and NLRP3 inflammasome has an impact on the production of IL-1β [32]. Activated macrophages can differentiate into two distinct phenotypes, namely the classically activated M1 type and alternatively activated M2 type, in response to different stimuli. The former is characterized by high levels of pro-inflammatory cytokines as well as active nitrogen and reactive oxygen intermediates. However, M2 macrophages can reduce the production of pro-inflammatory cytokines and increase the synthesis of important mediators in tissue remodeling, angiogenesis, and wound repair by phagocytosing apoptotic neutrophils, thereby participating in inflammation resolution [33]. Macrophages play a critical role in the pathogenesis of rheumatoid arthritis. The phenotypic diversity of macrophages contributes to their differential involvement in various rheumatic diseases [34]. In BD, the M1 pro-inflammatory phenotype predominates, rendering it an M1-driven disorder. Furthermore, impaired anti-inflammatory function mediated by IL-10-expressing M2 macrophages is implicated in the development and progression of Behçet's disease [35]. Studies have demonstrated that serum factors from patients with Behçet's disease can trigger classical pro-inflammatory activation of human peripheral blood macrophages, which may be associated with the inflammatory changes observed in this condition [36]. Notably, the M1 phenotype and M1/M2 ratio were also significantly increased in a mouse model of Behçet's disease induced by herpes simplex virus (HSV) [37]. Pro-inflammatory factors such as TNF-α, IL-1b, IL-6, IL-8, and IL-12 secreted by M1 macrophages and anti-inflammatory factors such as IL-10 secreted by M2 macrophages are closely related to BD [38]. Wu et al. found that differentially expressed genes in macrophages treated with BD and HC serum were enriched in the nuclear factor kappaB (NF-κB) signaling pathway, suggesting that macrophages are polarized toward a proinflammatory M1-like phenotype through NF-κB signaling [39]. In recent years, genome-wide association studies (GWAS) and other large-scale genetic studies have found that HLA-B*51, -A*03, -B*15, -B*27, -B*49, -B*57 and -A*26 are independently associated with the risk of BD [40]. In addition, nearly 20 loci as the disease susceptibility genes, such as C-C chemokine receptor 1 (CCR1), ERAP1, IL23R and IL-10, are associated with the risk of BD [41, 42]. Interestingly, BD-associated CCR1 and IL10 loci can promote polarization of M1 macrophages [43]. Interestingly, M1 and M2 type can be transformed into each other under the influence of microenvironment. However, the specific role of this transformation in the pathogenesis of BD remains unclear. In conclusion, correcting the imbalance between macrophage polarization or altering macrophage function is a promising therapeutic strategy for BD patients in the future.

Neutrophils in BD

Neutrophils and monocytes constitute the major phagocyte population and are the first line of innate defense [44]. There is some controversy in studies of phagocyte activity in BD. Yoshida et al. found that serum from patients with BD contains priming factors that enhance the production of superoxide by neutrophils [45]. But Eksioglu-Demiralp et al. showed that stimulated neutrophils from BD patients had reduced oxidative burst and, interestingly, no difference in phagocytic activity was observed between BD patients and HC [46]. The stimulation index of oxidative burst in neutrophils from active BD patients was significantly decreased after PMA stimulation. This was inhibited by the nitric oxide synthase inhibitor, and BD inhibited more neutrophil oxidative burst than HC. However, phagocytic activity did not differ between the two groups. It is possible that BD neutrophils are depleted in vivo [47]. Perazzio et al. found no significant differences between the BD group and the HC group in terms of oxidation bursts, phagocytic activity, microbicidal activity, or cytokine production. However, compared with patients with mild BD, cells with severe BD showed significantly higher oxidative burst activity both before and after PMA stimulation [48]. CD40 Ligand (CD40L), a glycoprotein expressed on the surface of activated helper T cells, basophils, mast cells, and eosinophils, is a member of the TNF family. Natural human soluble CD40L (sCD40L) is trimer, is the main source of platelet activation, but the activation of T cells, macrophages, endothelial cells and smooth muscle cells can also help sCD40L production [49]. sCD40L can stimulate the activation of leucocyte specific β2 integrin Mac-1 in neutrophils, thereby further promoting neutrophilic adhesion and migration. It can also strongly stimulate neutrophil oxidation bursts through CD40-dependent PI3K/NF-κB pathway [50]. Although no differences were observed in platelet activation and platelet-leukocyte aggregate formation between BD patients and HCs. However, BD patients had higher levels of sCD40L released from plasma and platelets. The release of sCD40L from platelets was mediated by Matrix metalloproteinase (MMP) -9, and the expression of MMP-9 was up-regulated by sCD40L in MEG-01 cell line. This will help in BD observed proinflammatory state [51]. During early inflammation stages, neutrophil activation and infiltration occur in affected organs leading to vasculitis via Neutrophil Extracellular Traps (NETs) release [52]. BD NETs not only induce the secretion of IL-8 and TNF-α by macrophages, but also facilitate the differentiation of IFN-γ+CD4+T cells [53]. sCD40L

may induce plasma NET release and stimulate oxidative burst in patients with active BD [54]. As noted above, the potential role of soluble factors in phagocyte activation remains controversial [55].

Natural killer (NK) cells in BD

NK cells are granular innate lymphoid cells that regulate the activity of other components of the innate and adaptive immune system through their cytolytic capacity and production of cytokines and chemokines, and participate in the immune response to autoimmune diseases [56, 57]. Based on the surface density of CD56 labeling, NK cells can be identified as two major NK cell subsets: $CD56^{bright}$ and $CD56^{dim}$. The $CD56^{dim}$ NK cell subset produce large amounts of granzyme B and perforin, which is more naturally cytotoxic, while the $CD56^{bright}$ subset is capable of producing abundant cytokines, especially IFN-γ, upon monocyte activation [58]. Studies have shown that the activity of NK cells in peripheral blood of patients with active BD was decreased while the actual number of NK cells is significantly increased. However, NK cell activity was significantly enhanced after the addition of INF-α [59]. However, the proliferation of NK cells is significantly increased in BD patients [60]. The levels of IFN-γ and IL-17 of $CD56^{dim}$ NK cell subset in BD were increased, and the levels of IL-4 were decreased, among which IL-17 may play a role in neutrophilic infiltration [61]. Studies have found that the proportion and cytotoxicity of NK cells in bronchoalveolar lavage (BAL) of BD patients with lung involvement are lower than those of controls [62]. NKG2D is an activated immune receptor expressed on the surface of NK cells and T cells. NKG2D-expressing NK cells are increased in BD patients, and the expression level of NKG2D is positively correlated with the BDCAF score [63]. In addition, NK cells can be divided into NK1, NK2, NK17 and NKreg according to their cytokine production. The NK1/NK2 ratio is increased and the number of NK17 cells and the IL-10-secreting NKreg cells is decreased in BD patients with only mucocutaneous involvement [64]. The expression levels of NK1-related cytokines (TNF-α, IFN-γ and IL-2) in NK cells increased in BD patients with uveitis recurrence stage, while NK2-related cytokines (IL-4 and IL-10) increased in remission stage [65]. CD107a is a marker of NK cells degranulation and is associated with target cells lysis mediated by NK cells. NK cells expressed a high level of CD107a in BD and had high cytotoxic potential [66]. In addition, co-culture of NK cells and T cells revealed that NK cells from inactive BD patients could inhibit IFN-γ secretion by CD4+T cells derived from active BD patients [67]. Regulating the activity and proliferation of NK cells and regulating NK cell subsets may be effective measures to control the symptoms of BD.

T cells in BD

T helper (Th) cells play a pivotal role in modulating immune responses. After differentiation and maturation in the thymus, T cells are subsequently transported via the humoral circulation to various immune organs throughout the body [68]. T cells can be divided into two subsets: CD4+T cells and CD8+T cells. According to their distinct functional properties, CD4+T cells can be classified into regulatory T cells (Tregs) and conventional effector T cells (Tconvs). The latter can further differentiate into Th1, Th2, and Th17 subsets based on the cytokines they produce [69, 70].

Interference with T cell homeostasis, especially the expansion of Th1 and Th17 and the reduction of Treg regulation, is considered to be the cornerstone of BD pathogenesis [71]. The interaction between HLA-B51 and endoplasmic reticulum aminopeptidase 1 (ERAP1) in antigen-presenting cells disrupts T cell homeostasis, resulting in the down-regulation of Treg and up-regulation of Th1 and Th17. This dysregulation can lead to overactivation of innate immunity, ultimately manifesting as symptoms [72]. ERAP1-Hap10, a variant ERAP1 with low enzymatic activity, is involved in the pathogenesis of BD through generating HLA-B51-restricted peptides, resulting in changes in immune dominance of CD8 T cell response [73].

A large number of studies have shown that Th1 plays a leading role in the immune pathogenesis of BD and plays a direct role in the skin and mucosal lesions of BD patients [74]. The level of T cell regulator IL-12 was correlated with BD activity, suggesting that Th1 type immune response plays a pathogenic role in active disease [75]. Compared with HC, Th1 cytokines, IL-12, IFN-γ, TNF-α and Th1-related chemokine receptors CCR5 and CXCR3 were increased in BD patients [76]. Correspondingly, Th2 type immune response also dominance in the active phase of BD [77]. Th2 (IL-4, IL-6 and IL-10) cytokines were highly expressed in BD patients [78]. The frequencies of type 1 (IL-2, IFN-γ) cytokine-producing CD4+and CD8+T cells in peripheral blood were significantly increased in active patients [79]. Sever studies have shown that in addition to the Th1 immune response in BD, the Th17 immune response also plays a decisive role and is related to the active inflammation of BD [80]. The IL17/IL23 pathway plays an important role in BD [81]. Th17 cells belong to CD4+effector T cells, which mainly secrete IL-17 A, IL-17 F, IL-22 and TNF-α to regulate inflammation. The differentiation and maturation of Th17 cells can be induced by IL-6, IL-23,

IL-1β and TGF-β [82]. Th17 cells can recruit neutrophils to the inflammatory site and mediate the hyperreactivity of BD neutrophils by secreting cytokines such as IL-17 [83]. The absolute number of Th9 cells was also significantly increased in BD and correlated with disease activity [84]. On the contrary, the benign effect of Tregs on BD was found in the study. After the transfer of CD4+CD25+Treg cells from normal mice into HSV-1 induced BD mice, the symptoms of BD model mice were improved, while the down-regulation of CD25+T cells made the symptoms worse [85].

Innate immunity and expression imbalance of Th1- and Th17-related cytokines play an important role in the pathogenesis and severity of BD [86]. Circulating Treg levels were found to be negatively correlated with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and BD current activity Form (BDCAF). Treg cells were significantly increased after IL-2 treatment, alleviating the progression of the disease [87]. T cell immunoglobulin mucin (TIM)-4 siRNA treatment also upregulated Treg count and improved symptoms and reduced BD severity scores in BD mice [88]. The increased proportion of Th17 cells and the decrease of Treg cells may be the related factors of BD [89]. The study by Guillaume et al. suggested a significant increase in Th17 cells and a decrease in CD4+forkhead box P3(+) regulatory Tregs in the peripheral blood of BD patients. Both are induced by IL-21 and correlate with BD activity [90]. Similarly, Anne et al. found that the Th17/Th1 cell ratio was significantly increased in the BD group compared with HC, and the ratio was higher in BD patients with uveitis or folliculitis [91]. Whole-genome microarray analysis showed that JAK/STAT signaling pathway was activated in both CD14+monocytes and CD4+lymphocytes in BD, and JAK1/STAT3 signaling pathway may be activated by Th1/Th17-type cytokines such as IL-2, IFN-γ, IL-6, IL-17 and IL-23 [92].

CD8+T cells, as classical major histocompatibility complex (MHC) class I antigen peptide presenting cells, were significantly increased in peripheral blood of BD patients [93]. However, there are few studies on the role of CD8+T cells in the pathogenesis of BD. The expression levels of CD11a and CD11c are significantly increased in patients with active BD, which may be a target for BD control [94].

γδ T cells are a unique type of T cells whose surface T cell receptors are composed of γ and δ chains. Although γδ T cells account for a small proportion of T cells, they play an important role in a variety of immune responses and immunopathology [95]. γδ T cells can be divided into Vδ1 T cells, Vδ2 T cells and Vδ3 T cells according to the expression of δ chain of T cell receptor on the surface of γδ T cells [96]. Compared with HC, the proportion of γδ T cells in the peripheral blood of BD patients was significantly increased, and γδ T cells could induce the production of IFN-γ and TNF-α [93]. Similarly, CD45RA+Vγ9+Vδ2+γδ T cells were found to be increased in BD, and CD45RA+γδ T cells could produce large amounts of TNF [97]. Compared with HC, patients with BD have an increased proportion of circulating γδ T cells, including CD8+or CD56+subsets. It is also associated with mucocutaneous lesions, but not with HLA-B51 [98]. Upon dimethylallyl pyrophosphate induction, the proportion of Vγ9/ Vδ2 T cells carrying TNF receptor II and IL-12 receptor β1 was increased in active BD [99]. Gram A (GrA), a serine protease with trypsin-like activity, is elevated in the plasma of patients with active BD and in the culture supernatants of Vγ9/Vδ2 T cells. Vγ9/Vδ2 T cells express perforin and granzyme and are involved in the pathogenesis of the disease through their degranulation and granzyme release [100]. γδ T cells increased in the PBMC of patients with active BD. Compared with the control group, the number of T cell receptors γδ+cells in BD patients was increased under the stimulation of oral ulcer culture microbial supernatant in BD patients [101]. However, the expression of γδ T cells in BD patients remains controversial. *Gunes et al.*. found that γδ T cells were not significantly increased in BD patients compared with HC, but the proportion of Vδ2+T cells was significantly reduced [102]. This contradiction may be caused by peripheral environment, disease activity and other factors, which needs to be verified by further research.

Treatment

Some drugs have been investigated for their ability to regulate the differentiation and function of immune cells in order to mitigate the progression of BD. For instance, curcumin has been shown to significantly downregulate the expression and production of inflammatory cytokines such as IL-6 and TNF-a in M1 macrophages from patients with Behçet's disease, thereby reducing inflammation [103]. Cyclosporine A (CsA) decreases the secretion of IL-17 and IFN-γ by activated PBMCs in patients with active uveitis BD [104]. The expression of Th2 cell response-related cytokines, such as IL-4, IL-10, and IL-13, increases in anti-CD3/anti-CD40 stimulated PBMCs from BD patients. Interestingly, Th1 cell response-related molecules exhibit inconsistency; while levels of IL-2 remain almost normal, those of IFN-γ and IL12 are significantly reduced [105]. Colchicine treatment can impede spontaneous NET formation in neutrophils, decrease MHR levels, and increase LMR levels [19, 52]. Azathioprine can reduce peripheral blood NK cell counts in BD patients

and has an independent consumption effect on them [66]. Due to the increasing research on the pathogenesis of BD, many new therapeutic targets for BD have been proposed. In particular, biological therapies offer the possibility of interfering with specific pathogenic pathways. Infliximab, an anti- TNF-α chimeric monoclonal antibody, can inhibit the expansion of Vγ9/ Vδ2 T cells, suppresses TNFRII expression and granzyme A release, and diminishes perforin and IFN-γ content in BD patients [106]. IL6 is a proinflammatory cytokine secreted by mononuclear phagocytes, T cells and activated astrocytes. It has been found that cerebrospinal fluid (CSF) IL-6 levels correlate with disease activity in neuro-BD (NBD) and can effectively predict long-term prognosis [107]. Based on the high level of IL-6 expression in CSF, IL-6 inhibitors have become a new therapeutic target and have been successfully used in NBD [108]. In addition, BD patients with ocular involvement have higher levels of IL-6 not only in serum but also in aqueous humor [109]. A large number of studies have found that Tocilizumab, a human anti-IL-6 receptor antibody, has a significant effect on ocular, neurological and vascular types of BD [110–113].

JAK/STAT signaling pathway has received increasing attention in the pathogenesis of autoimmune diseases. JAK inhibitors have become a new therapeutic target for autoimmune diseases, including BD [114]. The JAK1/STAT3 signaling pathway is activated in BD [92]. In recent years, lymphocyte targeted therapy has been applied to BD. It was found that the number of activated and memory B cell subsets increased in BD patients compared with HC, although there was no significant change in the total number of B cells [115]. B cells are also an important source of IL-6. Rituximab (RTX) is a monoclonal antibody that selectively targets B cells. It is effective in BD refractory ocular involvement [116]. CD52 antigen is present on lymphocytes and macrophages. Treatment with a T-cell-depleting anti-CD52 antibody therapy (CAMPATH 1-H) resulted in long-term treatment-free retrials in the majority of patients. However, there were adverse reactions such as cytokine release syndrome [117].

In BD-activated T cells, upregulated expression of the short form of cellular FLIP (cFLIP), Bcl-x(L), IKK, and IkappaB was observed. NF-κB activation may regulate the expression of antiapoptotic genes. Thalidomide and NF-κB small interfering RNA downregulated the expression levels of cFLIP and Bcl-x(L), and sensitised BD-activated T cells to CD95-induced apoptosis [118]. The NF-κB pathway plays a decisive role in monogenic BD-like autoinflammation. A20, also known as tumor necrosis factor α-induced protein 3 (TNFAIP3), is a cytosolic zinc finger protein induced directly by TNF-α/TNFR signaling [119]. It can act as a negative regulator of inflammation and immunity by inhibiting the NF-κB signaling pathway downstream of TNFR [120]. Haploinsufficiency of A20 (HA20) caused by a loss of function mutation in the TNFAIP3 (A20) gene is an autosomal dominant autoinflammatory disease characterized by Behçet -like disease symptoms [121]. In vitro studies have shown that A20 expression is reduced in CD4+T cells from patients with active BD. A20 silencing can promote the transformation of CD4+T cells to Th1 and Th17 phenotypes and significantly increased the levels of Il-1β and IL-6. It also inhibited the expression of anti-inflammatory cytokines IL-10 and IL-27. In addition, silencing A20 in retinal pigment epithelium (RPE) cells promoted the production of IL-6, IL-8 and MCP-1. In an experimental model of uveitis, local A20 overexpression could protect the integrity of the blood-retinal barrier and inhibit CD4+T cell activation, thereby significantly improving the severity of EAU. This is consistent with the maintenance of blood–retinal barrier (BRB) integrity and inhibition of CD4+T cell activation [122]. A20 expression was significantly decreased in PBMCs and dendritic cells (DCs) obtained from BD patients with active uveitis compared with normal controls. However, knockdown of A20 in DC had no effect on cell surface markers such as CD40, CD80, CD83, CD86 and HLA-DR [123]. A20 may play an anti-inflammatory role by regulating the NF-κB and MAPKs pathways [122]. There is no standard protocol for the treatment of HA20, and colchicine has some effect in mild cases of HA20 [124]. However, relatively severe cases seem to be more inclined to use biological agents such as anti-TNF-α agents and anti-IL-6 agents [125]. RELA (p65) is one of the five transcription factors in the NF-κB family. Like HA20, RELA haploid dysfunction also shows BD-like changes, resulting in decreased NF-κB signaling. Glucocorticoids, colchicine, and TNF inhibitors may benefit patients with RELA-associated autoinflammatory disease [126, 127]. Due to the exploration of the pathogenesis of BD, a variety of directions are provided for new therapeutic targets for BD.

Conclusion

In general, immune cells play a decisive role in the immunopathological mechanism of BD, whether it is innate immune cells or adaptive immune cells (Fig. 1). Significant progress has been made in understanding the pathogenesis of BD through the study of immune cells. By modulating the function of these immune cells, effective control over the onset and progression of BD can be achieved. Reducing monocyte aggregation, inhibiting over-activation of these cells, reducing the neutrophil hyperactivity and occurrence of NETs,

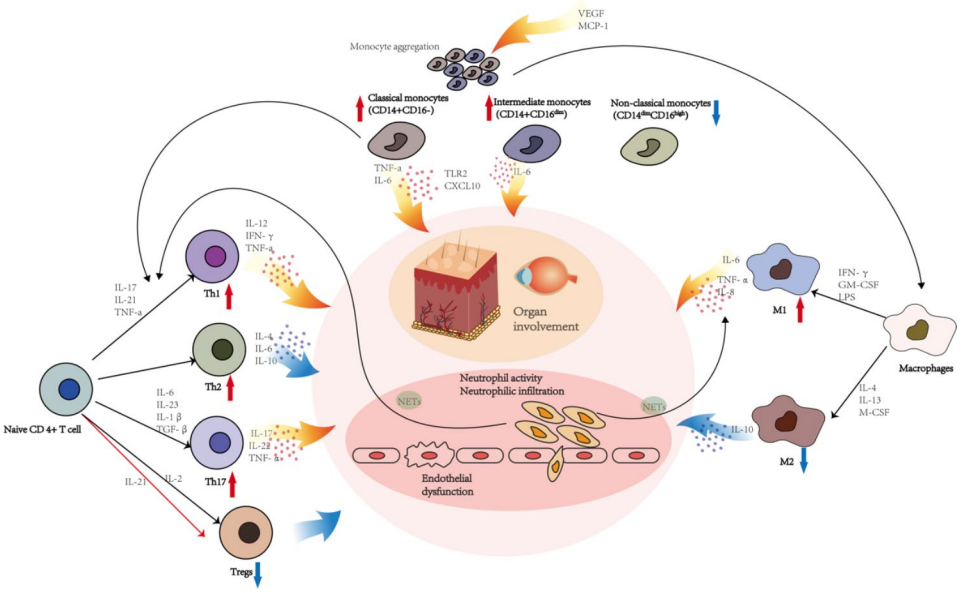

Fig. 1 Possible mechanisms of immune cell role in the pathogenesis of BD. In BD patients, the number of classical monocytes, intermediate monocytes, M1-type macrophages, Th1, Th2 and Th17 cells increased, and the pro-inflammatory factors secreted by these cells, such as IL-6 and TNF-a, caused neutrophils infiltration and endothelial cell damage, as well as organ damage. NETs released by neutrophils promote Th1 differentiation and macrophage secretion of IL-8 and TNF-α. However, the number of non-classical monocytes, M2-type macrophages and Tregs were decreased, and these cells play a role in the repair and remission of the disease. Various pro-inflammatory factors play a certain role in cell differentiation. IL-2 can amplify Treg cells, and Th17 cell differentiation increases and Tregs decrease under the induction of IL-21. In addition, VEGF and MCP-1 can promote monocyte aggregation. All kinds of cells and their cytokines act synergistically on BD

Table 1 Regulation of related cytokines in BD

Cells	Cytokines	biological relevance and functional impact	References
Monocytes	TNF-a	Classical monocytes in patients with BD can promote TNF-a production and promote Th1 differentiation.	[10]
	sCD14	sCD14 increased the adhesion of normal neutrophils to the monolayer of endothelial cells.	[12]
	TLR2	Monocytes may produce neutrophil-stimulated proinflammatory factors through TLR2 that play a role in BD.	[14]
	VEGF, MCP-1	VEGF and MCP-1 levels were significantly elevated in BD patients with thrombosis, which promoted the aggregation and adhesion of monocytes.	[23]
	FcγRIIb, FcγRIII	Low expression of FcγRIIb and high expression of FcγRIII in monocytes of BD patients may lead to overactivation of BD monocytes.	[26]
	CXCL10	Post-transcriptional dysregulation of CXCL10 mRNA may lead to an aggravation of BD characteristic inflammatory response.	[28]
	P2×7r	P2×7r activation significantly increases IL-1β release from LPS-stimulated BD monocytes, and TNF-α can up-regulate the expression and function of P2×7r in monocytes.	[30]
	UA	Uric acid (UA) can significantly increase the activity levels of NO, IL-1β and caspase-1 in peripheral blood monocytes of BD patients, aggravating the development of BD.	[31]
Macrophages	IL-10, CCR1	BD-associated CCR1 and IL10 loci can promote polarization of M1 macrophages.	[35, 43]
T cells	IL-17	Th17 cells can recruit neutrophils to the inflammatory site and mediate the hyperreactivity of BD neutrophils by secreting cytokines such as IL-17.	[83]
	IL-2	Treg cells were significantly increased after IL-2 treatment, alleviating the progression of the disease.	[87]
	IL-21	IL-21 induced the increase of Th17 cells and the decrease of regulatory Tregs in peripheral blood of BD patients.	[90]
	INF-α	The activity of NK cells in peripheral blood of patients with active BD was significantly enhanced after the addition of INF-α.	[59]
NK cells	IL-17	The levels of IL-17 of $CD56^{dim}$ NK cell subset in BD may play a role in neutrophilic infiltration.	[61]
Neutrophils	sCD40L	BD patients release higher levels of sCD40L, which promotes neutrophil adhesion and migration. It can also stimulate a burst of neutrophil oxidation	[50, 51, 54]

and inducing macrophage polarization towards the anti-inflammatory M2 phenotype can effectively mitigate inflammation in Behçet's disease. Th1 and Th17 cytokines play a pivotal role in the pathogenesis of BD inflammation, while Treg cells exert reparative effects on this condition. The focus is to rebalance Th1, Th2, and Treg in BD patients for treatment purposes. In active stages of the disease, NK cells in BD patients tend towards an NK1 phenotype while during remission they lean towards an NK2 phenotype; this suggests that subsets of NK cells are closely linked with the disease. Furthermore, regulating T cell activation and NK cell activity can help control BD. The intricate and intertwined cytokine network is intimately linked to the onset and progression of BD. As such, certain cytokines may serve as a novel therapeutic target for managing BD (Table 1). However, the precise mechanism of action of some immune cells in this disease remains controversial, and the pathogenesis of BD cannot be attributed to a single immune process but rather represents a complex interplay between multiple immune processes. The interaction and mechanism among immune cells remain elusive and require further investigation.

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Authors' contributions
DH conceived and wrote the manuscript. JLG conceived and reviewed the manuscript. All authors read and approved the final manuscript.

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