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REVIEW ARTICLE

Behçet disease (BD) and BD-like clinical phenotypes: NF-κB pathway in mucosal ulcerating diseases

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ABSTRACT

Behçet's disease (BD) is a heterogeneous multi-organ disorder in search of a unified pathophysiological theory and classification. The disease frequently has overlapping features resembling other disease clusters, such as vasculitides, spondyloarthritides and thrombophilias with similar genetic risk variants, namely *HLA-B*51*, *ERAP1*, *IL-10*, *IL-23R*. Many of the BD manifestations, such as unprovoked recurrent episodes of inflammation and increased expression of IL-1, IL-6 and TNFα, overlap with those of the hereditary monogenic autoinflammatory syndromes, positioning BD at the crossroads between autoimmune and autoinflammatory syndromes. BD-like disease associates with various inborn errors of immunity, including familial Mediterranean fever, conditions related to dysregulated NF-κB activation (e.g. *TNFAIP3*, *NFKB1*, *OTULIN*, *RELA*, *IKBKG*) and either constitutional trisomy 8 or acquired trisomy 8 in myelodysplastic syndromes. We review here the recent advances in the immunopathology of BD, BD-like diseases and the NF-κB pathway suggesting new elements in the elusive BD etiopathogenesis.

Keywords: Behçet's disease, NF-κB pathway, chromosome 8 trisomy, phagocytes, HLA-B51, autoinflammatory syndrome, NFKB1, TNFAIP3, RELA, IKBKB, IKBKG.

Introduction

Behçet's disease (BD) is an idiopathic systemic vasculitis initially described by Hulusi Behçet [1] and Benediktos Adamantiades [2] in the 1930s as recurrent oral and genital ulcers, associated with anterior uveitis with hypopyon. The disease frequently affects young adults and classically exhibits a geographic distribution throughout the ancient "Silk Road", with highest prevalence in Turkey, Iran and Japan [3]. BD lacks several features of classical autoimmune diseases, including female predominance, association with Raynaud's phenomenon, secondary Sjögren's syndrome, disease-specific and specific autoantibodies. Autoinflammatory syndromes, a subclass of inborn errors of immunity (IEI) [4], refer to seemingly unprovoked recurrent episodes of spontaneous innate immunity activation without usual hallmarks of autoimmunity (i.e., autoantibodies and antigen-specific autoreactive T and B cells). However, BD shares various genetic risk factors with autoimmune diseases, spondyloarthropathies and vasculitides, which we briefly review. Likely, BD is also an autoinflammatory disease with shared etiopathogenesis [5]. This is further supported by the clinical overlap between BD with familial Mediterranean fever (FMF) [6] and with conditions due to dysregulated NF-κB activation [7]. We will review recent advances on BD etiopathogenesis with special emphasis on comparison to novel monogenic diseases with autoinflammatory features that display overlap with BD, and include an overview of the NF-κB (nuclear factor kappa light polypeptide gene enhancer in B-cells) pathway.

Genetic risk factors

Associations between autoimmune diseases or autoantibody production and specific alleles of human leucocyte antigens (HLA) in the major histocompatibility region (MHC) region are well known. However, the mechanisms that mediate such susceptibility remain elusive. *HLA-B*51* is the strongest known identified genetic risk factor and responsible for 19% of the genetic susceptibility to BD [8, 9]. This association has been observed among several ethnic groups in GWAS studies [9, 10] imparting a 6-fold higher risk to develop BD [9, 11, 12]. The worldwide distribution of *HLA-B*51* follows the ancient "Silk Road" [13, 14]. HLA-B*51 has a low affinity for peptides and hypothetically slow protein folding may have a role in BD pathogenesis through the unfolded protein response [15]. Killer Ig-like receptor DL1 (KIR3DL1), a polymorphic inhibitory receptor, interacts with HLA-B*51. *KIR3DL1* allotypes seem further to modulate the clinical BD phenotype, potentially through NK cytotoxicity [16-18]. The low prevalence of HLA-

B*51 in many patients with *bone fide* disease, especially in non-endemic regions, suggests other factors must also be operative in BD or acting in epistasis.

ERAP1 is a locus found in epistasis with HLA-B*51 [19]. *ERAP1*, encodes endoplasmic reticulum associated aminopeptidase-1 (ERAP1), a zinc metallopeptidase inducible by IFNγ representing the M1 aminopeptidase family. ERAP1 further processes proteasome-derived peptides, especially those with a hydrophobic C-terminal amino acid, reducing them to 8-9 residues, the optimal length of binding onto MHC class I molecules (e.g., HLA-B*51 and B*27) [19, 20]. Finally, the antigenic peptide repertoires are presented to $CD8^+$ T cells (Figure 1). A recent GWAS showed that an *ERAP1* haplotype, encoding both p.R725G and p.D575N in strong linkage disequilibrium, conferred an increased risk for BD, mainly in HLA-B*51-positive patients or those with uveitis [17]. Surprisingly, homozygosity for *ERAP1* variants is a risk factor for BD, but is protective against ankylosing spondylitis [21] and psoriasis [22]. This was further confirmed in a Spanish cohort [23]. The repertoires of MHC-bound peptides are altered in *ERAP1*-deficient mice [24]. Thus, BD homozygotes for these variants may have altered presented peptide repertoires. Interestingly, the ERAP1 crystal structure shows that the variant p.R725G can affect substrate sequence or specificity and reduce the enzymes activity [25, 26].

Beyond the B*51 allele

Like in most autoimmune disorders, several non-HLA genes are associated with BD. Besides the MHC class I region, two other major risk loci are shared with spondyloarthritides, namely *IL23R* and *IL10*. In a GWAS, five single nucleotide polymorphisms (SNPs) of *IL-10* were strongly associated with BD [11, 12]. They were located in the promoter region and in the first, second and third introns, and in strong linkage disequilibrium with each other. Findings expanded previous results showing increased prevalence of *IL-10* promoter polymorphisms in BD patients [27]. Functional tests showed lower IL-10 production after lipopolysaccharide stimulation by variant carriers, suggesting that low regulatory cytokine IL-10 expression may be a risk factor for BD [12]. IL-10 inhibits costimulatory activity of macrophages for T and NK cell activation and IL-1β, IL-6, IL-12, TNFα and IFNγ production. Analogous to *ERAP1*, SNPs immediately flanking the *IL-10* gene have also been associated with inflammatory bowel disease [28] while *IL-10R* mutations abrogating IL-10 receptor signaling are associated with very early-onset inflammatory bowel disease [29]. These inflammatory bowel diseases display phenotypic overlap with BD. [30].

Another group of BD susceptibility loci includes the proinflammatory IL-12 cytokine family. IL-12 is a heterodimeric cytokine that shares its p40 subunit with IL-23 and plays an important role in Th1 responses, NK cell cytotoxicity and IFNγ production. A recent meta-analysis with two Turkish cohorts and 369 unrelated BD patients from 18 different geographic origins showed that an intronic variant in *IL-12A,* rs17810546, conferred a 1.7-fold increased risk for BD [31]. This result was replicated in a large cohort of Iranian patients [30]. Other variants relevant to this pathway were found in the intergenic region between *IL-23R* and *IL-12RB2* in BD patients of European-descent and Asian populations [11, 12]. *IL-23R* encodes a subunit of the IL23 receptor capable of stimulating Th17 cell proliferation and increasing the production of IL-1β, IL-6, IL-17 and TNFα [32]. Interestingly, BD variants were closer to the *IL-23R* side of the hotspot. The association of *IL-23R* is similar to ankylosing spondylitis [33], psoriasis [34] and inflammatory bowel disease [35], clinical conditions that share phenotypic manifestations with BD. Thus, these findings provide evidence that abnormalities in the genetic control of cytokine levels may be relevant in the pathogenesis of BD in some groups of patients.

A putative role of genetic and environmental factors for BD is yet to be described. There is some evidence regarding the role of microorganisms on BD, such as the hyperreactivity against *Streptococcus sanguinis* antigens and the homology [36-38]. In addition, *Staphylococcus aureus* and some *Prevotella* species have also been identified as potential candidates [39]. However, a very unusual genetic-environment interaction of *FUT2* variants was previously reported [20, 40, 41]. *FUT2* variants (W143X and p.I129F) were associated with BD, for which homozygosity is also associated with distinct composition of gut microbiome and predisposition or resistance to different infectious agents, implicating microbial–host interface in disease pathogenesis.

Familial Behçet's disease susceptibility loci

Most BD cases are sporadic, suggesting polygenic influence. However, familial clustering of BD occurs within a prevalence of 5-10% of the cases [42-47]. In a highly interesting study on 193 individuals from 28 multi-case families of Turkish origin, evidence for linkage was obtained in 16 chromosome regions: 1p36, 4p15, 5q12, 5q23, 6p22-24, 6q16, 6q25-26, 7p21, 10q24, 12p12-13, 12q13, 16q12, 16q21-23, 17p13, 20q12-13 and Xq26-28 [43]. The strongest linkages were observed for 12p12-13 and 6p22-24, the latter contains *TNFAIP3*, a known regulator of the NF-κB pathway. Interestingly, the above-listed regions contain multiple genes

encoding factors in NF-κB pathway (e.g., *CHUK*/*IKBKA*, *TRADD*, *TP53*, *BIRC7*, *IKBKG/NEMO*), while many of the others encode genes taking part in NF-κB activation and downstream signaling (e.g., *TNFSF1A*, *NOD2*, *NFATC2*, *NFATC3*). Rare variants in components upstream of NF-κB have also been found in BD patients by targeted deep sequencing of *TLR-4*, FMF (autosomal recessive *MEFV*) and *NOD2* genes [92]. The frequency of the most penetrant p.M694V mutation of *MEFV* was found to be increased in Turkish BD patients, again suggesting an overlap between these two conditions [5]. Dysregulation of the NF-κβ pathway is a common finding in disorders with BD or BD-like phenotypes, especially those in the field of NF-κB-related autoinflammatory diseases [48].

New insights: NF-κB pathway mutations

The NF-κB pathway has been increasingly implicated in BD as several monogenic BD-like phenotypes have been identified [49]. NF-κB has also been directly shown to play a crucial role in the pathogenesis of BD. Todaro et al [50] showed a paradoxical CD95 hyperexpression in BD T cells associated with an insensitivity to CD95-induced apoptosis, probably attributable to the inhibitory action of antiapoptotic genes and mediated by IKKα/β and IκB upregulation, culminating with an increase on NF-κB translocation to the nucleus. Interestingly, immunosuppressant therapies, like thalidomide, re-sensitized BD activated T cells to CD95-induced apoptosis and reversed all the abnormalities. Our group has previously reported that the inflammatory characteristics of BD could be associated with NF-κB hyper activation in cells from BD patients, given the constitutive over-expression of phosphorylated p65 subunit [51]. Taken together, these data suggest that NF-κB contributes to the regulation of the apoptosis-related factors and pro-inflammatory signals in BD cells (Figure 2). Several components of the NF-κB pathway have been specifically examined in BD or BD-like diseases that exemplify this concept [48].

NFKB1

A previous study provided evidence that the –94ins⁄del ATTG promoter polymorphism of *NFKB1* encoding p105/p50 may have functional consequences in BD, especially in patients with ocular involvement [52]. Yenmis et al [53] expanded this finding by showing that the wild-

type rs696 polymorphism of *NFKBIA*, which results in miR449a-induced decreased expression of IκBα (nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha) [54], is also strongly associated with an enhanced risk of BD in Turkish patients. We recently reported a monogenic form of BD-like features in carriers of an *NFKB1/p50* p.H67R variant with reduced nuclear entry of p50 and decreased transcriptional activity in luciferase reporter assays [55]. Intriguingly, patients with p.R157X had almost complete NF-κβ1 loss due to proteasome degradation of both the truncated and wild type protein (likely as a dimer) and displayed extreme pathergy-like hyperinflammatory responses (familial autoinflammatory necrotizing fasciitis) to minor surgery, due to enhanced macrophage inflammasome activation. Minor trauma may also incite pyoderma gangrenosum lesions in such patients [55, 56].

Tumor necrosis factor, α–induced protein 3 (*TNFAIP3*) and *OTULIN*

TNFAIP3 encodes the NF-κB regulatory protein A20, a potent inhibitor of the NF-κB signaling pathway. *TNFAIP3* SNPs were demonstrated to confer risk for BD in Chinese [57] and Japanese [58] patients, whose mononuclear cells produced large amounts of IL-1β, IL-6 and TNFα after stimulation [58]. Moreover, Zhou et al [59] reported on five families of different ethnicities carrying six distinct high-penetrance heterozygous germline *TNFAIP3* mutations, mainly located at the A20 ovarian tumor domain. Patients developed autoinflammatory disorders resembling BD, presenting with oral/genital ulcers, gastrointestinal involvement and pathergy. Furthermore, mutant A20 are likely to act through haploinsufficiency and patient-derived cells showed increased degradation of IκBα and nuclear translocation of the NF-κB p65 subunit together with increased expression of NF-κB-mediated proinflammatory cytokines. Indeed, whole exome sequencing in familial BD has now found several families with dominant loss of function mutations in *TNFAIP3 [58, 60-64]*.

Simultaneously, the same group also identified two missense and one frameshift *OTULIN* autosomal recessive mutations in three distinct families with four affected patients with an BD-resembling autoinflammatory phenotype [65]. Patients presented with neonatal-onset fever, neutrophilic dermatitis or severe panniculitis and failure to thrive, but without obvious primary immunodeficiency, culminating with a clinical condition named Otulipenia. Both OTULIN and A20 are important gatekeepers of innate immunity by cleaving activating polyubiquitin chains generated by the linear ubiquitin assembly complex (LUBAC) and A20 on various target proteins in the NF-κB canonical pathway targets [66].

LUBAC-mediated ubiquitination is critical for regulation of immune signaling and cell death, mainly stimulating the IκB kinase (IKK) complex. Interestingly, absence of LUBAC function represented by *HOIL1* [67] or *HOIP* [68] subcomponent deficiencies attenuate NF-κB signaling and patients present with apparently paradoxical features of susceptibility to infection, due to hypogammaglobulinemia, and systemic autoinflammation with fever, high concentrations of acute-phase reactants, hepatosplenomegaly and lymphadenopathy. The former manifestation is secondary to lymphocytes and fibroblasts impaired IL-1β and CD40 activation and the latter is probably due to a yet unclear increased responsiveness to IL-1β in monocytes (Figure 2).

NF-κB essential modulator (*NEMO*)

Incontinentia pigmenti (IP) is a rare X-linked dominantly inherited genodermatosis caused by *NEMO* mutations in females, as affected males usually do not survive until birth. Two case reports showed the concurrence of IP with sporadic BD [69, 70] and two additional independent reports showed that at least heterozygous NEMO p.D406V mutation can cause familial BD in female family members [7, 71]. Interestingly, Takada et al [7] could not observe skewed X-chromosome inactivation in peripheral blood mononuclear cells nor in oral or intestinal mucosa in these patients. Despite the apparent absence of any mechanistic study with D406V BD carriers, we hypothesize that this mutation may be associated with *NEMO* loss-of-function, ultimately culminating with an increased IκBα degradation and, consequently, NF-κB hyperactivity. Previous studies have found splice variants causing truncations in the *IKBKG/NEMO* transcripts leading to an expressed truncated protein, increased infections and decreased NF-κB activity [72, 73]. Alternatively, NEMO deleted exon 5–autoinflammatory syndrome (NEMO-NDAS) was also recently characterized with panniculitis, chorioretinitis, progressive B cell lymphopenia and hypogammaglobulinemia, and a high interferon gene signature [73]. The autoinflammatory features described in NEMO deficiency, including arthritis, colitis, and graft versus host disease (GVHD)-like dermatitis, are thought to be a failure of the C-terminus of NEMO to recruit the A20/TNFAIP3, thus losing the negative regulation of the pathway [74].

RELA (p65)

A recently published study described a family with an autosomal-dominant mucocutaneous ulceration whose proband was dependent on anti-TNF therapy for sustained remission [75]. A heterozygous mutation of *RELA* (c.559+1G>A), encoding the NF-κB subunit RelA, alters the canonical donor splice site downstream of exon 6 and showed segregation with the disease phenotype. Interestingly, the patients' fibroblasts exhibited increased apoptosis in response to TNFα, impaired NF-κB activation and defective expression of NF-κB–dependent antiapoptotic genes, whereas the patients' PBMC were relatively spared of such abnormalities. Furthermore, *RelA*$^{+/-}$ mice develop cutaneous ulceration and similarly impaired NF-κB activation. Although merely linked to a single BD-like clinical manifestation, these findings are another piece of data in the puzzling hypothesis associating BD and the NF-κB pathway.

Chromosome 8 trisomy and the risk of BD

The clinical phenotype associated with constitutional trisomy 8 is pleiotropic, variably with developmental delay, joint contractures, deep palmar and plantar creases, *corpus callosum* agenesis, skeletal and renal anomalies [76]. These germline cases usually harbor a constitutional trisomy 8 mosaicism (CT8M) pattern, with only some cell lines presenting chromosomal abnormality. There is a well-recognized association between CT8M and malignancies, in particular hematological myeloid malignancies and myelodysplastic syndrome (MDS) [77]. Alternatively, acquired trisomy 8 is also associated with hematologic malignancies and leukemia generally with a poor prognosis. BD has been increasingly associated both with CT8M [76, 78-80] and the acquired form secondary to myelodysplastic syndromes [81-86]. Our group recently found a patient with CT8M with refractory BD-like symptoms (namely, severe oral ulcers, intermittent fevers and abdominal pain with ulcerative inflammatory bowel changes) causing failure to thrive, despite immunosuppression, including anti-TNF and anti-IL-1 therapies (unpublished data). Due to refractory BD and the risk of progression to MDS, bone marrow transplantation was performed. In two years follow up, neither BD-like symptoms nor MDS have recurred.

The precise pathogenesis of MDS is unknown, but it is suggested that immune dysregulation may play a role in the bone marrow failure, which might explain these systemic inflammatory findings as well [87]. The percentage of MDS patients with BD-like symptoms who displayed trisomy 8 was reported to be about 94.7%, which is much higher than the 37-53% of MDS patients with other cytogenetic aberrations [88]. Additionally, Lin et al [86] reported that 14 of 19 (73.7%) patients with MDS and BD-like symptoms had trisomy 8. A recent systematic

literature review demonstrated that trisomy 8 seemed to correlate with BD features with an increased frequency of fever and erythema nodosum suggesting the existence of a "trisomy 8 syndrome" in these patients [89]. To date, the association between trisomy 8 and features of BD is also poorly understood. Ripperger et al [90] reported the smallest gain of chromosome 8 in CT8M cases with malignancies so far, reducing the alleged critical region to 8p11.21-q11.21 harboring 31 genes possibly associated with these manifestations. Intriguingly, these include the inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta (*IKBKB*).

Activation of IKKβ, the protein product of *IKBKB*, stimulates anti-apoptotic, pro-inflammatory and proliferative pathways via NF-κB activation. Notably, site-specific expression of constitutively hyper active IKKβ was sufficient to induce acute pancreatitis [91], myositis/muscle wasting [92, 93] and hepatitis [93] in mice models. Interestingly, local and systemic production of proinflammatory cytokines, including IL-6, IL-1β and TNFα, was increased in such animals, once again resembling autoinflammatory features. In contrast, epidermis-specific *IKBKB* knockout mice show inflammatory signs of NF-κB hyper activation and can develop psoriasis-like lesions [94], also observed in p65 and c-Rel deletions [95]. The exact mechanism of disease initiation remains unclear in this disorder, but ablation of these components from epidermal keratinocytes seems to interfere with this balance and triggers an inflammatory response that is marked by the induction of inflammatory cytokines such as IL-1β and TNFα by NF-κB. Therefore, although speculative, the evidence above suggests that *IKBKB* can contribute to activation of the NF-κB signaling pathway, which, in turn, has received special attention recently due to new insights about BD pathophysiology.

Issues on BD classification

BD is a heterogeneous disease which can affect virtually any organ systems, making its classification challenging. Autoantibodies are usually not evident in BD and there are no universally accepted diagnostic markers, forcing the physician to primarily rely on clinical criteria [96, 97]. Even though a positive pathergy test is considered suggestive for a BD diagnosis, its positivity not only vary widely in different populations and with different methodology used, but some data also indicate that its sensitivity is decreasing over time [98]. BD is considered to be a primary vasculitis, but it has been also argued to belong to the group of spondyloarthritides [99]. More recently, the autoinflammatory features of BD and the role of innate immunity have received

increasing attention and currently many consider BD to be in the crossroad of autoimmune and autoinflammatory diseases. Taken together, it is understandable why perhaps no other disease has given rise to as many classification criteria as BD and why some authors advocate there are clustered phenotypes possibly representing different disorders within one single condition [100].

The vasculitis spectrum

BD is classified among inflammatory vascular diseases, but has no predilection for specific type, affecting vessels of all kinds and sizes [101]. Although vascular injury is common, the pattern of vascular involvement is unique as BD lacks necrotizing vasculitis of small arteries (typical in antineutrophil cytoplasmic antibody-associated vasculitides), giant cells in large vessels (e.g., Takayasu arteritis), and immune complex-type cutaneous venulitis [102]. In some patients, antibodies against endothelial cell α-enolase have been identified. Their significance is not clear, but they may have implications in particular in patients with cardiovascular involvement [103]. Furthermore, little evidence exists for vasculitis in some common BD manifestations, such as pseudofolliculitis and central nervous system lesions [104].

On the other hand, the diffuse inflammatory disease in all layers of the large veins characteristically involving substantial segments of the vessel wall and the vasculitis of the *vasa vasorum*, culminating with the formation of pseudoaneurysms of large arteries are singular among the primary vasculitis and are important links with this family of disorders [102]. Of note, the pulmonary artery aneurysms specific to this condition are still associated with bad prognosis and constitute one of the main causes of mortality in BD.

BD as a spondyloarthritis

Based on clinical features, Moll et al [99] back in the 1970s proposed the concept of "seronegative spondyloarthritides" and included BD in this classification. Since then, much has been debated regarding this topic, as BD patients rarely exhibit sacroiliitis [105] and, even though the disorder is associated with MHC class I, classical association is with HLA-B*51 rather than HLA-B*27 [106]. In contrast, several similarities suggest shared pathogenesis including the overlapping extra-articular clinical manifestations (uveitis, erythema nodosum and gastrointestinal involvement); the good response to TNFα blockade therapy [107]; and the recent association of both BD and inflammatory intestinal diseases with *IL-23R* and *IL-10* polymorphisms [11, 12]. In addition, some evidence suggests a role of microorganisms in BD similarly to reactive arthritis.

The pro coagulative aspect

Thrombosis is observed in 10-37% of BD patients, mainly in venous (superficial and deep) vessels, although arterial disease is a serious cause of morbidity and mortality, especially when it involves the pulmonary arteries [108, 109]. Nonetheless, some caveats persist regarding the etiopathogenesis of such pro coagulative state evident in BD. Some authors consider a pivotal role for impaired endothelial function, while others advocate that a subjacent thrombophilic factor is responsible for the thrombotic phenomena. Interestingly, despite the high frequency of rare thrombotic conditions (namely multiple thrombotic sites, thrombophlebitis or even intracardiac thrombosis), thromboembolic events are rare. This paradox can be explained by the high adherence of thrombi to the diseased veins [102]. In fact, this is the main argument used to justify the better response to immunosuppressants rather than anti-coagulation alone and to explain the low success rate of vascular interventions observed on thrombotic manifestations [110]. Furthermore, a progressive reduction of endothelial progenitor cells has already been described in BD patients, representing a mechanism of induction and amplification of vascular injury [111].

Differences in prevalence of vascular involvement are observed according to the geographic distribution, especially regarding arterial disease. This suggests a putative role of yet unknown genetic and environmental factors [112]. In large studies investigating the presence of thrombophilic factors as a leading cause of thrombosis in BD, no prevalence differences were found in different pro thrombotic factors (i.e., factor V Leiden, prothrombin G20210A polymorphism, MTHFR C677T polymorphism, factor VIII, anticardiolipin and anti-β2-glycoprotein I antibodies) between BD patients with or without thrombosis [113-116]. In addition, high thrombomodulin levels in BD [117] have strong correlation with pathergy phenomenon [118], although these abnormalities do not correlate with the occurrence of thrombotic events in the disorder. In summary, the mechanisms of thrombosis in BD are still unclear. However, based on the data presented above, thrombosis in BD may result from a combination of disorders in procoagulants, anticoagulants and fibrinolytic factors with the underlying vasculitis and endothelial injury [119].

Skin manifestations and interplay with other neutrophilic dermatoses

Clinical features of BD frequently involve the skin and overlap with those observed with monogenic BD-like diseases. BD cutaneous manifestations frequently involve dense

neutrophilic inflammation. Erythema nodosum-like lesions are seen mostly in females and occur in one-third of patients with a typical clinical presentation of bilateral pretibial, painful, erythematous nodules. Papulopustular lesions usually occur on the trunk, buttocks and lower limbs, and consist of sterile folliculitis- or acne-like lesions on an erythematous base. Superficial thrombophlebitis and the pathergy reaction complete the most frequent BD-associated skin manifestations [120]. Although not common, recurrent extragenital ulcers that heal with scarring are among the most specific cutaneous findings of BD. Extragenital ulcers can be seen on various locations such as the legs, axillae, breast, interdigital skin of the foot, and neck.

Despite the vasculitic and thrombotic histopathological findings of BD in other organs, mucocutaneous lesions, namely oral ulcers, genital ulcers, erythema nodosum-like lesions, superficial thrombophlebitis, and papulopustular lesions do not always present with vasculitic features histopathologically. As a rule, histopathological assessment of early cutaneous lesions usually has features of a leukocytoclastic vasculitis, while later/established lesions may demonstrate a lymphocytic nodular perivasculitis or vasculopathy.

The neutrophilic dermatoses (ND) are a heterogeneous group of non-infectious systemic syndromes characterized by the predominance of non-neoplastic neutrophilic inflammatory infiltrates in the skin, potential for extracutaneous involvement and a frequent association with multi-systemic diseases [121-123]. ND include acute febrile neutrophilic dermatosis [Sweet's syndrome (SS)], pyoderma gangrenosum (PG) and BD. All the ND can demonstrate pathergy. Multiple ND can occur concurrently in the same patient. For instance, SS-like lesions may be observed together with BD. Compared to BD, skin lesions on other ND are usually larger (up to 12 cm in SS), in plaques, or ulcerated (as in PG) [123]. Non-BD ND only sporadically affect internal organs, unlike BD. ND can occur concurrently with other disorders, particularly myeloproliferative disorders, inflammatory bowel disease, spondyloarthritides, and other disease states, or be triggered by medications (such as granulocyte colony-stimulating factor). Neonatal SS often heralds a serious underlying disorder and requires thorough investigation for viral etiology, primary immunodeficiency, neonatal lupus syndrome, genetic [123, 124]. Therefore, a wide diagnostic approach is warranted when evaluating patients with ND.

The role of phagocyte hyperactivity

Clinical and pathological data such as the pathergy phenomenon strongly suggest that neutrophil hyperactivity to various even minor stimuli is a prominent feature in BD pathogenesis.

Among others, exacerbated neutrophil activity due to altered oxidative burst [125], chemotaxis [126], phagocytic and microbicide activities [127] have been described. Takeno et al [128] showed that reactive oxygen species (ROS) production is increased not only in BD patients but also in asymptomatic HLA-B*51 carriers and transgenic mice expressing HLA-B*51. Our group recently assessed the classical phagocyte functions (oxidative burst, *in vitro* cytokine production, phagocytic and microbicide activities) in BD patients [129]. Patients with severe BD exhibited phagocytic dysfunction and some evidence of constitutive activation, especially in oxidative burst activity. We found significant correlations between BD patients' activity score and constitutive or *Streptococcus sanguinis*-stimulated production of several cytokines (TNFα, IFNγ, IL-6, IL-23 and IL-8) by neutrophils and PBMC. The role of neutrophil extracellular traps (NET) release, active in neutrophil death [130], remains to be further studied in BD, while there is evidence for the role of NETosis in systemic lupus erythematosus [131], rheumatoid arthritis [132] and ANCA-associated vasculitides [133]. Our group recently showed an increased constitutive and a markedly soluble CD40L-stimulated NET release of BD patients [134].

Another class of phagocytic cells, monocytes, also bridge innate with adaptive immunity by processing and presenting antigens to T and B cells. Thus, it is reasonable to hypothesize that monocytes may play an important role in diseases with neutrophil hyperactivity. Yavuz et al [135] showed abnormal toll-like receptor (TLR)-2 and TLR-6 expression and response in neutrophils and monocytes of BD patients after *S. sanguinis* and its related heat-shock protein, HSP-60. Monocytes from BD and familial Mediterranean fever patients present higher oxidative burst activity than those from rheumatoid arthritis patients and healthy controls, especially when stimulated by sodium monourate crystals [136]. These data indicate innate immunity involvement with striking hyperresponsiveness of multiple phagocytic cell lines in BD.

Is BD an autoinflammatory disease?

Autoinflammatory diseases are inborn errors of the innate immune system and characterized by seemingly unprovoked episodes of sterile inflammation, fever and cytokine amplification (Table 1) [137, 138]. Monogenic autoinflammatory disorders classically develop early in childhood and have been associated mainly with the IL-1β, IL-18, TNFα, type I interferon (interferonopathies) and the NF-κB pathways. NF-κB acts downstream of these pro-inflammatory cytokines among other danger/stress signaling pathways and now there is an emergence of NF-κB monogenic autoinflammatory disorders as sequencing becomes more available. Several typical

findings in BD overlap with those in monogenic autoinflammatory (Table 2) [6, 102, 139-144]. Promising results with IL-1 targeted therapies in BD suggest that this disease may be in the spectrum of polygenic (or complex) autoinflammatory diseases [85, 86]. In addition, most NF-κB-related autoinflammatory diseases respond to anti-TNFα treatment, which is also observed on BD. Anti-TNFα are well-known efficacious and usually last line therapies for BD refractory or severe conditions, with some pieces of evidence for mucocutaneous [145], ocular [146], vascular [147], neurologic [148] and gastrointestinal manifestations [149]. Further characterization of the NF-kB pathway components, activation and regulation in more of these monogenic autoinflammatory disorders may help delineate clinical features in relation to the molecular pattern of NF-kB activation and may aid in designing novel therapies.

Conclusions

Understanding the pathogenesis of BD is a pivotal step for the development of novel and efficacious therapies. An abnormal innate hyperinflammatory response and neutrophil hyperactivity are well-known hallmarks of the disorder. However, since most BD patients display polygenic inheritance and wide clinical phenotypic heterogeneity, these impede the creation of both a reliable classification and a unified pathophysiologic theory. BD has several autoinflammatory features including recurrent self-limited manifestations overlapping with different classic and newer autoinflammatory disorders. Recent findings from monogenic diseases sharing features with BD strongly suggest a major role for dysregulated innate immunity activation due to mutations in the NF-kB pathway in familial BD patients while GWAS studies suggest rare polymorphisms in NF-kB pathway and its activator and effector genes in polygenic cases. Additional studies are needed for the full comprehension of the role of these processes in BD.

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TABLE LEGENDS AND FOOTNOTES

Table 1 – Main monogenic and polygenic autoinflammatory diseases described to date.

Abbreviations: APLAID, autoinflammation PLCG2 associated antibody deficiency and immune dysregulation; CAIN, C/EBPε-associated autoinflammation and immune impairment of neutrophils; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature**;** CRIA, cleavage-resistant RIPK1-induced autoinflammatory syndrome; DIRA, Deficiency of interleukin-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor [IL-36R] antagonist; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HA20, Haploinsufficiency of A20; IL-18PAP-MAS, IL-18-mediated pulmonary alveolar proteinosis and recurrent macrophage activation syndrome; MWS, Muckle-Wells syndrome; NEMO-NDAS, NEMO deleted exon 5–autoinflammatory syndrome; NFKB1-BLD and –FANF, NFKB1-associated Behçet-like disease and familial autoinflammatory necrotizing fasciitis; NLRC4-MAS, NLRC4 macrofage associated syndrome; NOMID, neonatal onset multisystem inflammatory disease; ORAS, otulin-related autoinflammatory syndrome; PAAND, Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne syndrome; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy; PFIT, pyrin activation in the autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia; PRAAS, proteasome-associated autoinflammatory syndromes; SAPHO, synovitis acne pustulosis hyperostosis osteitis; SAVI, STING-associated vasculopathy, infantile-onset; SIFD, congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay; TRAPS, Tumor necrosis factor receptor-associated periodic syndrome.

Table 2 – Overlap between manifestations of Behçet's disease and monogenic autoinflammatory diseases.

Abbreviations: CAIN, C/EBPε-associated autoinflammation and immune impairment of neutrophils; DIRA, Deficiency of interleukin-1 receptor antagonist; HA20, Haploinsufficiency of A20; NFKB1-BLD and –FANF, NFKB1-associated Behçet-like disease and familial autoinflammatory necrotizing fasciitis; PAAND, Pyrin-Associated Autoinflammation with

Neutrophilic Dermatosis; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne syndrome; TRAPS, Tumor necrosis factor receptor-associated periodic syndrome.

FIGURE LEGENDS

Figure 1 – Endoplasmic reticulum associated aminopeptidase-1 (ERAP1) mechanism of action. The enzyme is present inside the antigen presenting cell (APC) endoplasmic reticulum (ER) and works as fine editing scissors of proteasome-derived peptides, reducing them to 8-9 residues (the optimal length). Finally, it facilitates the binding onto histocompatibility leukocyte antigen (HLA) class I molecules, which will be ultimately presented to $CD8^+$ T cell receptor (TCR).

Figure 2 – A) Canonical and non-canonical NF-κB activation pathways. Canonical pathway is activated by TLR (Toll-like receptors), T cell receptor, B cell receptor and cytokine receptors (eg, TNFα, IL-1β, IL-6, amongst others) and initiates a cascade that culminates with IκB kinase (IKK) complex activation, represented by its three subunits: IKKα , IKKβ and IKKγ (NEMO, NF-κB essential modulator). Ubiquitin ligase activity of linear ubiquitin assembly complex (LUBAC), constituted mainly by HOIP, HOIL-1 and SHARPIN, is required for the efficient activation of IKK and subsequent phosphorylation of IκBα, which, in turn, is the signal for releasing NF-κB1, a dimer composed by p50 and RelA/p65. While OTULIN modulates the pathway by cleaving activating polyubiquitin chains generated by LUBAC, A20 acts on various target proteins. Similarly, phosphorylation and subsequent degradation of p105 is sufficient to modulate canonical NF-κB activation pathway by stimulating ERK (extracellular signal-regulated kinases) and releasing regulatory dimers of p50. Non-canonical pathway is usually activated by different receptors, such as LTβR (Lymphotoxin-β receptor), BAFF-R (B-cell activating factor receptor), CD40, CD27 or OX40. NIK (NF-κB-inducing kinase)-mediated activation of IKK complex induces phosphorylation and polyubiquitination of NF-κB2 (p100 and RelB), which are the signals for proteasomal degradation of p100 into the active subunit p52, culminating with NF-κB2 activation. B) Protein structure and mutation sites of the main NF-κB components (*NFKB1*, *TNFAIP3*, *NEMO, OTULIN, HOIP* and *HOIL1*) described in association with Behçet's disease.

Table 1 – Main monogenic and polygenic autoinflammatory diseases described to date.

Monogenic diseases		Polygenic diseases
Pyrin-associated diseases (FMF, PAAND)	CAIN	Crohn's disease
Cryopyrin-associated periodic syndrome (FCAS, MWS, NOMID)	NEMO-NDAS	Chronic recurrent multifocal osteomyelitis
TRAPS	NFKB1-BLD and -FANF	Systemic onset juvenile idiopathic arthritis
Mevalonate kinase deficiency	IL-18PAP-MAS	Behçet's disease
PAPA syndrome	SAVI	Gout
Blau syndrome	APLAID	Adult-onset Still's disease
Majeed syndrome	NLRP1-associated diseases	PFAPA syndrome
PRAAS/CANDLE	ORAS	SAPHO
DIRA/DITRA	SIFD	Ankylosing spondylitis
CRIA	PFIT	
HA20-BLD	NLRC4-MAS	

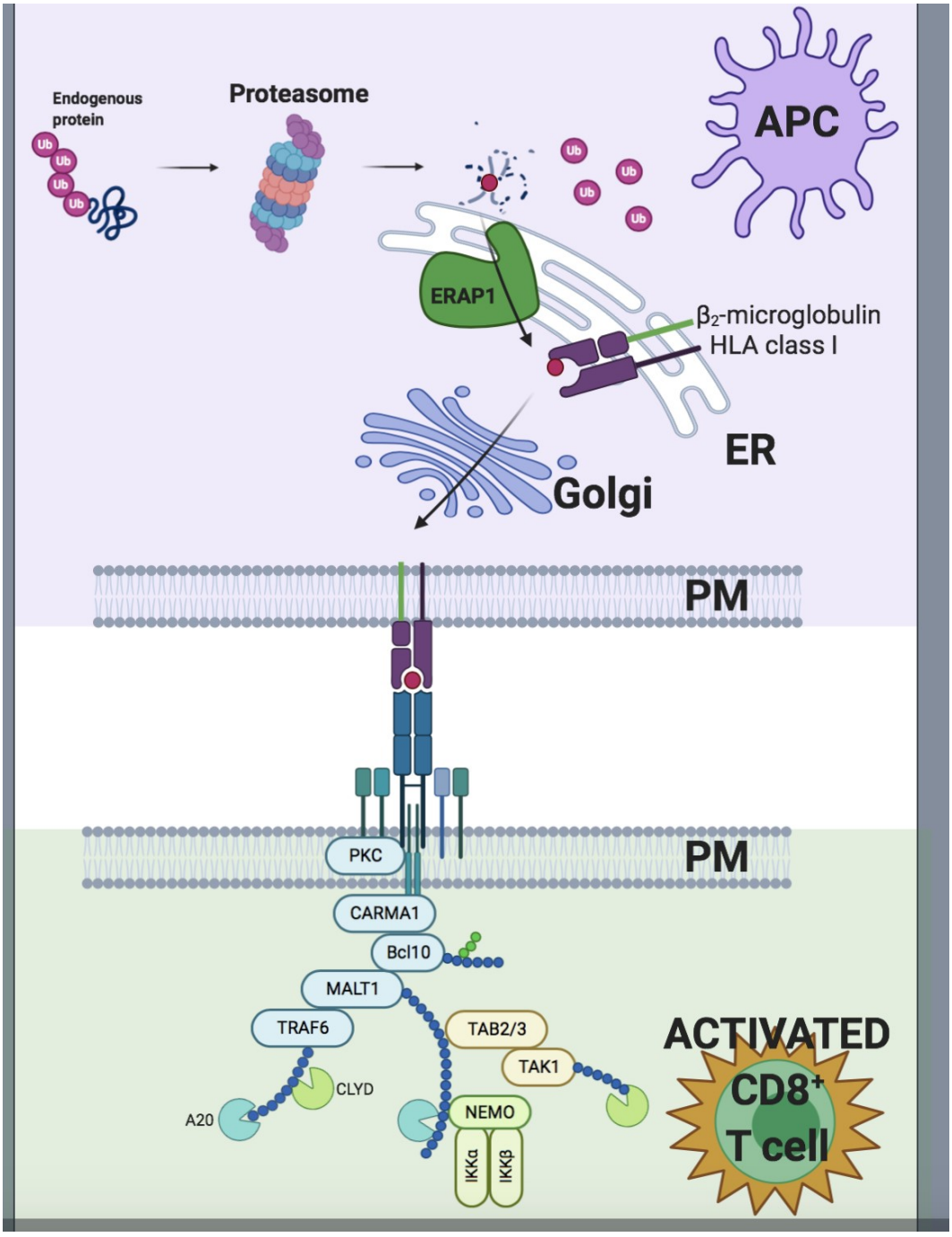
Abbreviations: APLAID, autoinflammation PLCG2 associated antibody deficiency and immune dysregulation; CAIN, C/EBPε-associated autoinflammation and immune impairment of neutrophils; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CRIA, cleavage-resistant RIPK1-induced autoinflammatory syndrome; DIRA, Deficiency of interleukin-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor [IL-36R] antagonist; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HA20, Haploinsufficiency of A20; IL-18PAP-MAS, IL-18-mediated pulmonary alveolar proteinosis and recurrent macrophage activation syndrome; MWS, Muckle-Wells syndrome; NEMO-NDAS, NEMO deleted exon 5–autoinflammatory syndrome; NFKB1-BLD and –FANF, NFKB1-associated Behçet-like disease and familial autoinflammatory necrotizing fasciitis; NLRC4-MAS, NLRC4 macrofage associated syndrome; NOMID, neonatal onset multisystem inflammatory disease; ORAS, otulin-related autoinflammatory syndrome; PAAND, Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne syndrome; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy; PFIT, pyrin activation in the autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia; PRAAS, proteasome-associated

autoinflammatory syndromes; SAPHO, synovitis acne pustulosis hyperostosis osteitis; SAVI, STING-associated vasculopathy, infantile-onset; SIFD, congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay; TRAPS, Tumor necrosis factor receptor-associated periodic syndrome.

Table 2 – Overlap between manifestations of Behçet's disease and monogenic autoinflammatory diseases.

Manifestation	Disease (gene)
Pathergy or other neutrophilic reaction to minor trauma	PAPA syndrome (*PSTPIP1*)
	HA20 (*TNFAIP3*)
	NFKB1-BLD, NFKB1-FAANF (*NFKB1*)
Oral/genital ulcers	Mevalonate kinase deficiency (*MVK*)
	Cryopyrin-associated periodic syndrome (*NLRP3*)
	TRAPS (*TNFRSF1A*)
	NFKB1-BLD (*NFKB1*)
	CAIN (*CEBPE*)
Uveitis	Blau syndrome (*NOD2*)
	Cryopyrin-associated periodic syndrome (*NLRP3)*
	TRAPS (*TNFRSF1A*)
Acne-like lesion	DIRA (*IL1RA*)
	PAPA (*PSTPIP1*)
	Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (*LPIN2*)
	PAAND (*MEFV*)

Abbreviations: CAIN, C/EBPε-associated autoinflammation and immune impairment of neutrophils; DIRA, Deficiency of interleukin-1 receptor antagonist; HA20, Haploinsufficiency of A20; NFKB1-BLD and –FANF, NFKB1-associated Behçet-like disease and familial autoinflammatory necrotizing fasciitis; PAAND, Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne syndrome; TRAPS, Tumor necrosis factor receptor-associated periodic syndrome.



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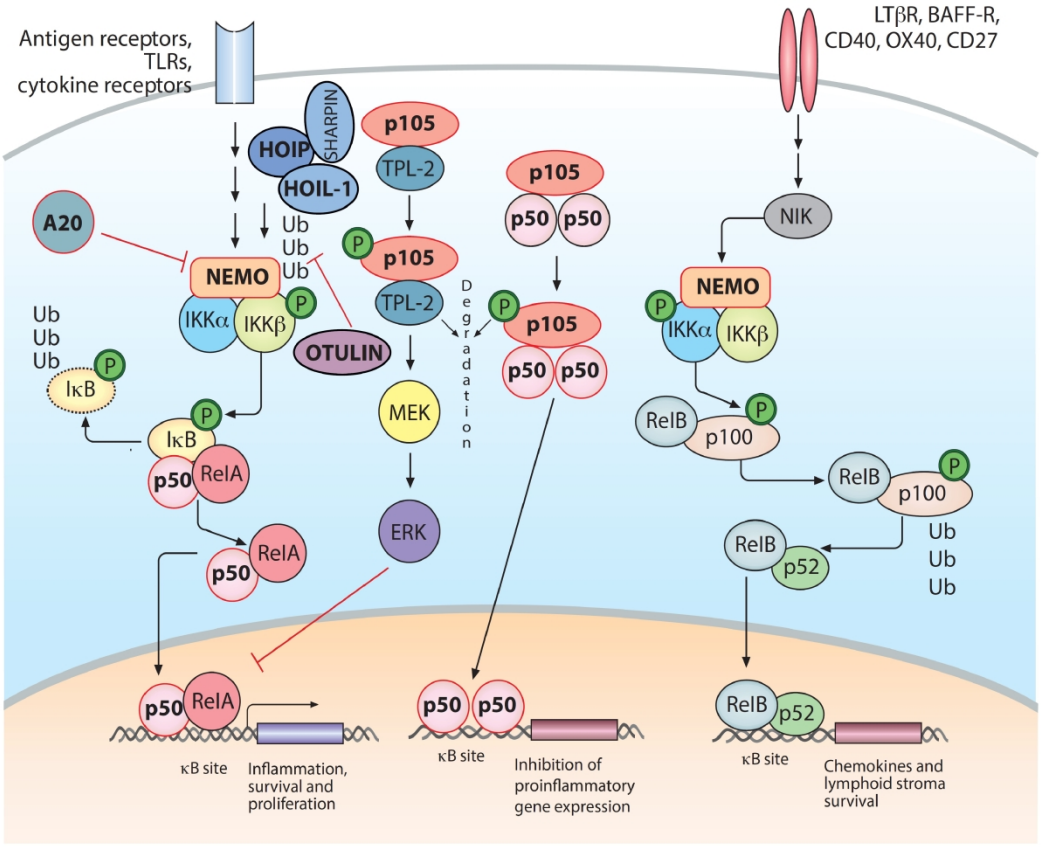

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