MINIREVIEW

The anti-Inflammatory activity of Interleukin-37 in Behçet's disease

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Received: October 09, 2016
Published online: November 21, 2016

Behçet's disease (BD), a systemic vasculitis disorder is associated with the Silk Road. Oral aphtous and genital ulcers, cutaneous pseudo folliculitis and uveitis are the most common manifestations. These manifestations are frequently associated with neurological symptoms, pulmonary involvement and arthritis. The etiology remains uncertain and the most fashionable hypothesis is immunological. BD disease is thought to be caused by pathogenic helper T (Th) cells. Th1, Th2, Th17 and Treg cells have been implicated in its pathogenesis. Recently spotlight has been drawn to novel cytokine of the IL-1 family: interleukin-37 (IL-37). Since its discovery, IL-37 has been studied extensively in immunological field. It has been established that IL-37 inhibits innate and adaptive immunity through suuppression of pro-inflammatory molecules. This review will discuss the role of IL-37 in BD.

Keywords: IL-37; Behçet's disease; Interleukin-1 family; inflammation; IL-17; IL-33

To cite this article: Agnès Hamzaoui, *et al*. The anti-Inflammatory activity of Interleukin-37 in Behçet's disease. Inflamm Cell Signal 2016; 3: e1452. doi: 10.14800/ics.1452.

Abbreviations: BD, Behçet's disease; Th, helper T cells; IL-37, interleukin-37; PBMCs; Peripheral blood mononuclear cells; TNF, tumor necrosis factor; WT, wild-type; MIP-2, macrophage inflammatory protein-2; M-CSF, macrophage colony-stimulating factor; GM-CSF, B-cell-attracting hemokine-1 granulocyte macrophage colony-stimulating; MCP-5, monocyte-chemoattractant protein-5; rIL-37, Recombinant IL-37; ROS, reactive oxygen species.

Introduction

Behçet's disease (BD) is a chronic relapsing/remitting multi-system disease of poorly understood aetiology, primarily characterised by oro-genital ulceration but also affecting other body systems including the eye, joints and skin [1, 2]. BD can be life-threatening in severe forms where the disease progresses to involve the large blood vessels, central nervous and pulmonary systems or the gastrointestinal tract. The disease is increased approximately six-fold in patients with HLA-B51/B5 genetic polymorphisms [3] and is widely regarded as an auto-inflammatory condition although autoimmune responses to certain specific antigen have been described in the disease [4]. Infection by herpes viruses family (EBV, HSV1) were also thought to be important in both the initiation and in triggering acute exacerbations of affected systems in BD [5, 6].

BD is considered a T-cell-mediated disease [7-9]. Although much has been learned during recent years on the pathogenesis, it is still an important cause of morbidity and mortality in the areas where it is prevalent. As BD lacks

specific symptoms and laboratory findings, the diagnosis relies on clinical criteria.

Immunological modifications modulate disease onset, progression and outcome of BD. Peripheral blood mononuclear cells (PBMCs) and inflammatory sites (skin lesions, cerebrospinal fluid, bronchoalveolar lavage) from patients with BD expressed dysregulated Th1/Th2, Th17/Treg ratios [10-11]. Multiple studies demonstrated that inflammatory mediators are highly expressed in patients with BD compared to healthy controls [12], mainly represented by Th1 and Th17 cells cytokines. In the same way, genetic polymorphisms of inflammatory mediators are associated with disease susceptibility and evolution [13].

The association of the IL-1 cluster gene polymorphisms with the development of BD was investigated [14] and lightened the field through characterization of new immunological parameters including pro-inflammatory agonists (IL-33) [15-18] and putative antagonists (IL-37) [19-20] mediators.

Functional analysis using neutralizing monoclonal antibodies treated human PBMCs indicated that the IL-1 family of cytokines might play an importantly role in the development of autoimmune/inflammatory diseases [21]. IL-37 is a newly discovered cytokines able to modulate innate immune cells that has been studied in several diseases regarding its anti-inflammatory capacity. The association of cytokines with BD on multiple levels promotes us to systematically review what had been published recently on the crucial nature of IL-37 in relation to the inflammation pathways gaining attention for its regulatory capability in this multisystemic disorder. The information obtained may lead to a better understanding of the insights into IL-37 in BD.

Biological functions of IL-37

Human PBMCs treated with the neutralizing monoclonal anti-IL-37 was able to increase inflammatory cytokines production, such as IL-1β, IL-6 and tumor necrosis factor (TNF)-α [22]. Similarly, PBMCs transfected with siRNA to IL-37 reduce the IL-37 protein abundance, leading to increases in the generation of IL-β, IL-6, and TNF-α when stimulated with LPS or Pam3CSK4 [22].

In IL-37 transgenic (IL-37tg) mice, bone marrow-induced DCs (BMDCs) stimulated with LPS exhibited a decreased expression of MHCII and CD40 expression compared with wild-type (WT) mice controls [23]. When syngeneic T cells, or allogeneic T cells were co-cultured with dendritic cells from wild type mice, proliferation of $CD4^+$ and $CD8^+$ T cells increased significantly. When splenic T cells cocultured with BMDCs from WT mice, there was induced expression of $CD4^+$ $CD25^+$ $Foxp3^+$ Treg cells. Notably, BMDCs from IL-37tg mice, promoted Treg cells expansion [23]. Mouse macrophage RAW cell line can stably express the human IL-37b isoform. IL-37b transfection effectively reduce LPS-stimulated TNF-α, macrophage inflammatory protein-2 (MIP-2), IL-1α and IL-6 expression in comparison with mock transfected RAW cells, and production of macrophage colony-stimulating factor (M-CSF), B-cell-attracting chemokine-1 (BCA-1), granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1β, monocyte-chemoattractant protein-5 (MCP-5), IL-23 was considerably reduced in IL-37 treated RAW cells [22]. The epithelial cell line A549 transfected with IL-37b down-regulated constitutive and IL-1β-induced IL-6 and IL-1α expression [23]. A549 cells or THP-1 cells transfected with IL-37b displayed colocalization of IL-37 and Smad3. IL-37b expressing RAW cells treated with Smad3 specific inhibitor SIS3 can reverse the inhibition of IL-6 and IL-1α expression, and THP-1 cells treated with SIS3 can up-regulate IL-1β expression. THP-1 cells depleted of Smad3 by lentiviral shRNA and then challenged with IL-37, showing with reduced expression of IL-1β or LPS induced IL-8, IL-6 [23]. Collectively, these data suggest that IL-37 plays an anti-inflammatory effect in human PBMCs, mice BMDCs, and regulates the production of inflammatory components in cell lines partly mediated by Smad3.

Recombinant IL-37 (rIL-37) suppressed joint inflammation, reduced cell influx and lowered histological scores in experimental arthritis [24]. Low doses of IL-37 (40 μg/kg) suppressed joint inflammation by 51.7% and significantly decreased synovial IL-1β by 84%, IL-6 by 73%, TNF-α by 33%, chemokine (C-X-C motif) ligand 1 by 58%, Chemokine (C-C motif) ligand 3 or macrophage inflammatory protein 1- alpha by 64%, IL-1a by 40% and MPO by 60%. The activity of IL-37 was associated with a lower recruitment of neutrophils into the joint [24].

IL-37 was also proposed as new therapeutic strategies that can be used as immunosuppressive anti-inflammatory cytokine in psoriasis and other inflammatory cutaneous diseases [25] reducing CXCL8, IL-6, and S100A7 levels.

IL-37 and its receptor

Human IL-37 is a member of the IL-1 gene family (Fig. 1). There are 11 members in the IL-1 family, seven of which are pro-inflammatory agonists and four of which are receptor antagonists. The agonists are involved in the innate immune system and are generated after Toll-like receptor stimulation [26-27]. Whether IL-37 is an antagonist or an agonist of the immune system is still not well defined, but studies have

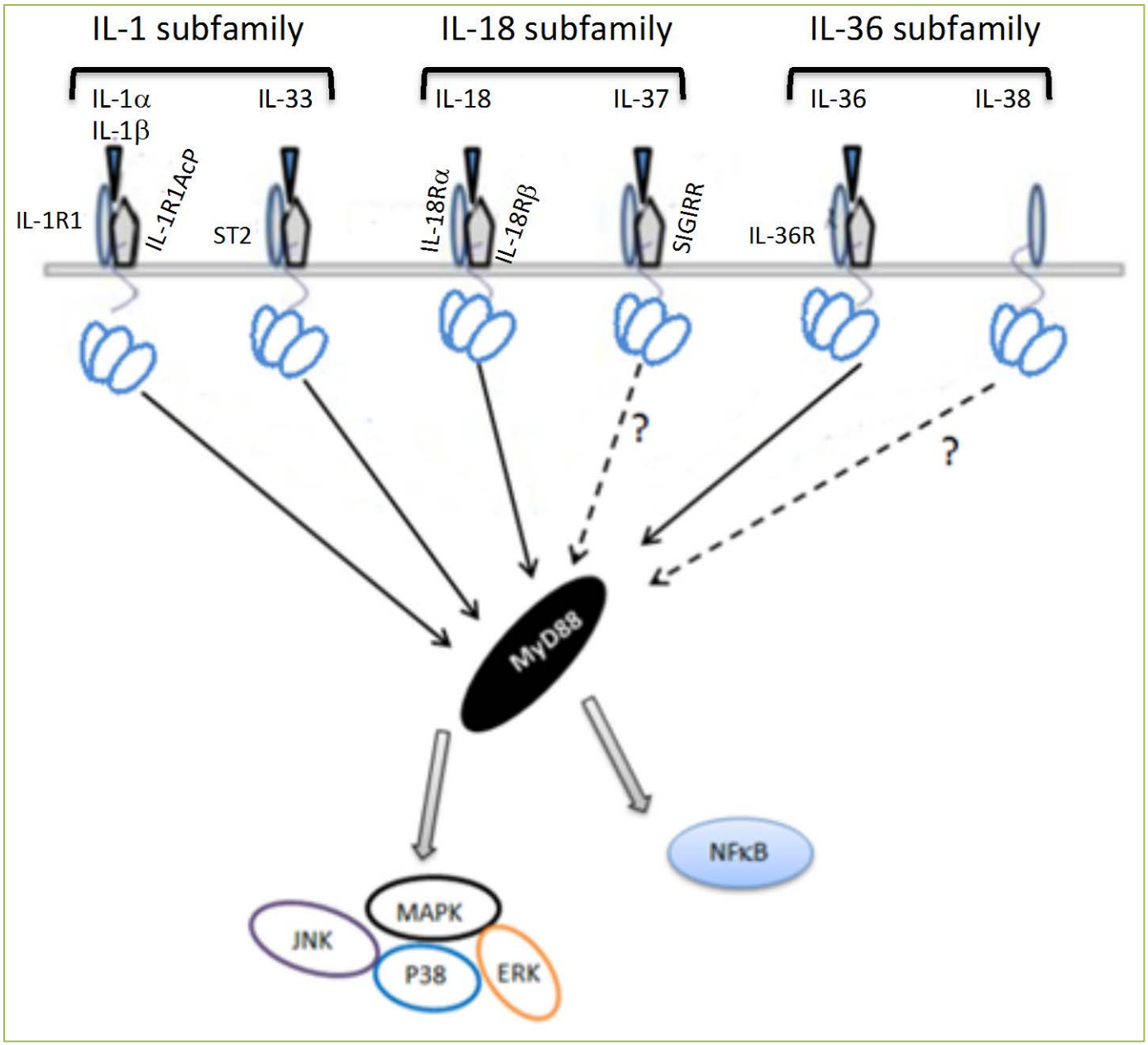

Figure 1. Model for IL-1 family signaling. IL-1 family is divided into three subfamilies based on the length of the N-terminal propieces, (**1**) IL-1 subfamily: IL-1α, IL-β, IL-1 receptor antagonist (IL-1Ra), and IL-33. (**2**) IL-18 subfamily: IL-18 and IL-37. (**3**) IL-36 subfamily: IL-36α, IL-36β, IL-36γ, and IL-38. The receptor for each IL-1 family cytokine is a heterodimer of the proper or common subunits. IL-1R1, ST2, IL-18Rα, and IL-36R are ligand-binding subunits, while IL-1R accessory protein (IL-1LRAcP), IL-18Rβ, SIGIRR (single immunoglobulin IL-1-related receptor) are signaling subunits. When IL-1 family cytokines bind to the corresponding ligands, they recruit the corresponding signaling receptor subunit, and therefore translocates nuclear factor- (NF-) κB to the nucleus and activates MAPKs (p38, JNK, ERK) pathways.

shown that it suppresses innate immune responses [28]. Based on their precursor's length and each precursor's propiece length, members of the IL-1 family are further divided into subfamilies: IL-1 subfamily, IL-18 subfamily, and IL-36 subfamily. IL-37 belongs to IL-18 subfamily (Figure 1). IL-1 subfamily has the longest propieces, and IL-18 subfamily has shorter ones. The mechanism of removal of its propiece is still not well known [29]. In humans, IL-37 gene can be found on chromosome 2 along with the genes from 8 other members of the IL-1 family. It is made up of 12 β-barrel strands, with an IL-1 family structural pattern that is closer to that of IL-18 [30]. There are five splice transcript variants for this interleukin that encode distinct isoforms (IL-37a-IL-37e) [30]. The largest of the isotypes is IL-37b, and it has 5 of the 6 exons. IL-37b is the isoform that is biologically functional and can produce homodimers; other isoforms are either not functional, or their function is undetermined [31 - 32].

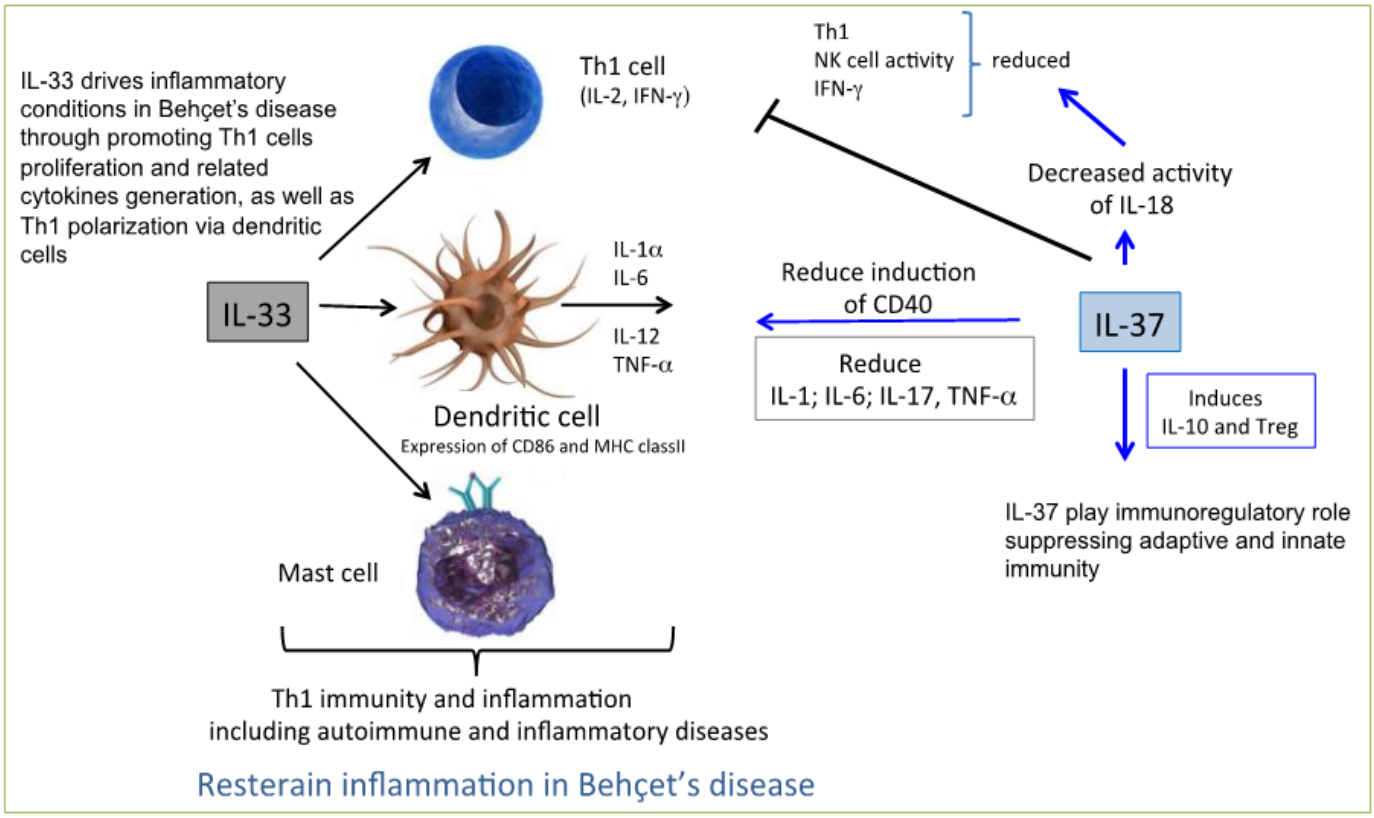

Figure 2. Schematic representation of the potential interactions between IL-33 and IL-37 in Th1 immunity in Behçet's disease. IL-33 drivers type 1 inflammatory conditions including Behçet's disease through promoting Th1 cells proliferation and related cytokines generation, as well as Th1 polarization via dendritic cell. By contrast IL-37 play immunoregulatory roles in Th1 immunity inducing IL-10 production and promoting regulatory T cells (Treg) proliferation and suppressing IL-17 synthesis and inhibiting IL-1α, TNF-α, IL-6.

Monocytes, macrophages, synovial cells, plasma cells as well as epithelial cells of the skin, and intestine expressed IL-37 protein. The abundance of IL-37 transcripts is low in PBMCs and DCs is due to an instability sequence in IL37. This instability sequence limits mRNA half-life of IL-37 [33]. Indeed, despite having a CMV promoter, resting mRNA levels for IL-37 in IL37-tg mice is either absent or low but rapidly increases with inflammation [23]. Despite low production, recombinant IL-37 is highly active, low concentrations of recombinant IL-37 were able to reduce LPS-induced IL-1β, IL-6, and TNF-α production in vitro [21; 33].

IL-37 in Behçet's Disease

There is no extensive investigation on IL-37 and its role in regard to its biological role in BD [19-20]. These features will be discussed in this short review.

There were lower levels of IL-37 in BD patients compared to healthy subjects [19-20]. IL-37 mRNAs expression and serum levels were decreased in BD patients compared to healthy controls. This inhibition was more pronounced in active BD patients suggesting its correlation with BD disease activity, a low level of IL-37 likely contributing to disease severity [19-20]. The decreased IL-37 level in BD was associated with increased production of IL-1β, IL-6, and TNF-α in LPS-stimulated PBMCs [19, 20]. In vitro experiments showed that addition of recombinant IL-37 (rIL-37) significantly suppressed the production of these 3 pro-inflammatory cytokines.

IL-37 exerted a more suppressive effect on IL-17 production in active BD patients than in healthy controls [19]. rIL-37-treated dendritic cells (DCs) in BD remarkably inhibited Th17 and Th1 cell responses as compared to control DCs [19, 20]. Pay *et al*. reported abnormalities in DCs from BD patients [34].

Treatment with steroids might be able to return the expression of IL-37 back to subnormal levels, particularly when drug was used at high doses. The restored IL-37 level in inactive BD was associated with regression of symptoms corresponding to clinical remission and inactive BD phase. Recent data from Ye *et al*. showed that rIL-37 significantly inhibited reactive oxygen species (ROS) production and promoted IL-27 production in association with a down-regulated activation of mitogen-activated protein

kinase (MAPK) in DCs [19]. In fact, rIL-37-treated DCs had a significant inhibitory effect on the Th1 and Th17 cytokine response. The decrease in IL-37 gene expression observed in patients with active BD could be responsible of DCs malfunctioning [19].

The perspectives of the potential therapeutic modality using IL-37 in inflammatory diseases

IL-37 expression was found increased in systemic lupus erythematosus (SLE) [35-37] and in RA synovial cells [38-41]. The reasons to this contrast in IL-37 expression between BD and other inflammatory conditions are not clear, but may be due to differences in the immunological mechanism reactions, inducing a particular and different "anticipative" immune system against inflammation.

Recent findings have revealed the therapeutic potential of IL-37 in inflammatory diseases. Active RA patients exhibited higher IL-37 levels compared with patients in remission and controls [42]. On the contrary, IL-17 and IL-17-driving cytokine production were markedly reduced in synovium and joint cells from CIA mice receiving injection of IL-37. ApoE-deficient diabetic mice injected with IL-37 showed significantly less calcification areas detected by both von Kossa and Alizarin Red staining, and much smaller plaque size of the atherosclerotic lesions and lower plaque vulnerability scores detected by hematoxylin-eosin staining in the aorta root [43]. Collectively, these data suggest the potential therapeutic modality using IL-37 in inflammatory diseases. Human IL-37 VAr2 exerts less inhibition on proinflammatory cytokine production than did other IL-37 variant. Conversely, purified extracellular IL-37 variant proteins demonstrated comparable inhibitory abilities in vitro. This study reveals that common genetic variants of IL37 lead to different immune-inhibitory potencies, primarily as a result of differences in IL-37 protein stability, suggesting the possible involvement of these variants in various human diseases.

Conclusions

Evaluating the important roles of IL-37 in regulating T cells, DCs began to shed an interesting light on the understanding of immune-pathologic mechanism in BD. Dysregulated IL-37 is observed in BD patients. In addition, functional analysis has showed that supplementing IL-37 in BD patients demonstrated development and push down inflammation. Since decreased protein and mRNA IL-37 levels correlate with BD susceptibility. An adequate manipulation of IL-37 pathway might be critical for regulating normal immune responses. With the advent of more advanced technology and emergence of more elegant studies in the future, the enhanced understanding of the molecular and cellular targets of IL-37 will be indeed helpful to interpret the pathogenesis of BD (Fig. 2).

Conflicting interests

The authors have declared that no competing interests exist.

Author contributions

AH and KH contributed equally to this work.

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