

Title

Mast Cells Mediate Skin Inflammation in Psoriasis: A New Therapeutic Approach with the Anti-inflammatory Cytokines IL-37, IL-38 or IL-1Ra

INTRODUCTION

Approximately 3% of the population of the United States of America and 2% of the whole world population suffer from psoriasis. The disease is associated with a high degree of morbidity, and the patients affected have a decreased quality of life. Psoriasis is a common disease that presents skin lesions, dysregulated immune system and chronic inflammation, problems that are still unresolved [1], although in recent years, biomedical research has made substantial advances in elucidating the pathogenic mechanisms. Predisposition to psoriasis may be due to environmental factors such as stress, drugs, microorganisms, smoking, and trauma, but also to the dysregulation of the immune system and, in particular, to the imbalance of some immune regulatory cytokines [2]. Psoriasis is an autoimmune-mediated disease that shows scaly patches on the skin and redness in the lesions, due to the increased numbers of capillaries, and can be transferred from transplant donor to recipient [3]. Psoriasis typically affects the scalp, elbows, sacral region and knees, but it can also occur throughout the body [4]. In particular, patients may present thickening of the epidermis, leukocyte infiltration and parakeratosis [5]. In the skin, cytokines produced by activated immune cells contribute to the induction of psoriasis [6]. The disease involves the immune cells including macrophages, mast cells (MCs), neutrophils and Th1, Th17, and Th22 lymphocytes, which contribute to epidermal proliferation and production of cytokines and chemokines [7]. In addition, around the capillaries of the dermis and epidermis T CD3⁺ and T CD8⁺ lymphocytes, and CD11c⁺ dendritic cells can be detected, which confirm the immunological intervention in this disease [8]. Moreover, studies have indicated that the numbers of MCs are increased in psoriatic skin, while the numbers of regulatory T (Treg) cells are not altered [9]. In fact, mice deficient of Treg cells develop a skin disease similar to psoriasis and show a decrease of IL-10 [10].

In psoriasis, keratinocyte cells of the innate immune system that respond early to the external insults in the body are particularly involved [11]. Dendritic cells, key sentinels of the immune system, are also increased in psoriatic lesions and favor the production of Th1 cells and secretion of pro-inflammatory cytokines and nitric oxide [12]. Dendritic cells, macrophages and MCs are activated through Toll-like receptor (TLR), leading to cytokine/chemokine production and induction of inflammation [13]. Cytokines IL-1, tumor necrosis factor (TNF) and IL-6 are secreted at the site of the lesion by keratinocytes and activate dendritic cells which, in turn, produce other cytokines such as IL-12 and IL-23, that lead to the differentiation of TH1 and TH17 cells, keratinocytes and MCs, which secrete IL-1, IL-6, TNF, IL-17 and IL-22, and also chemokines CXCL8, 9, 10, 11, and 20, mediating an inflammatory role [14] (Fig. 1). It is likely that blocking one of these steps above, may result in a relief of psoriasis [15].

Mast Cells (MCs)

It has been known for over one hundred years that MCs play an important role in the pathophysiology of skin diseases [16], however, the experiments that best describe the characteristics of MCs in immune and inflammatory processes mainly concern those carried out on mice. This was possible because MC-deficient mutant mice were created, offering the opportunity to study immune and inflammatory processes [17]. Immune cells, such as lymphocytes and macrophages, have subsets, but this is not the case for granulocytes including MCs, although some authors have divided MCs into subsets MC1 (anti-tumorigenic) and MC2 (pro-tumorigenic) [18]. In addition to this partition, we believe that MCs can be divided into two subpopulations with different functions, based on the number of granules of every single cell. However, the difference in function of these two groups of MCs has not yet been clearly defined.

MCs are of hematopoietic origin, derived from bone marrow cells, and reside in vascularized tissues [19]; they are sources of biologically active compounds including cytokines, and arachidonic acid products (prostaglandins and leukotrienes) which mediate inflammatory disorders [20]. IgE-dependent MC activation is a key reaction in allergic diseases and anaphylaxis [21]. Therefore,

MCs are activated by high affinity IgE that bind to the FcεRI receptor and lead to degranulation and immediate release (few seconds) of preformed chemical mediators and TNF also released from the granules [22] (Table 1). Subsequently (after several hours), there is a *de novo* synthesis of cytokine and chemokine. MCs intervene in many types of innate or adaptive immune responses [23] (Fig. 1). Macrophages and MCs generate caspase-1, as well as chymase, activate immature pro-IL-1 beta and transform it into mature IL-1 beta, which amplifies the inflammatory state [24]. The production of IL-1 from MCs increases the number of infiltrating neutrophils with the release of proteases and rising inflammation [25]. TNF is another highly inflammatory cytokine released by activated macrophages, and many other cells including MCs, which contain preformed TNF that can be released rapidly (after about 10 min) from the cell granules after activation by anti-IgE, or exposure to substance P (SP) or ultraviolet rays (as occurs in the skin) [26]. TNF can also be produced through the synthetic pathway which requires several hours. MCs can be recruited into inflamed skin by diverse chemotactic molecules (including Vascular endothelial growth factor (VEGF), stem cell factor (SCF) and a number of CC and CXC chemokines) produced by immune cells [27]. MCs have been proposed to influence many biological processes, including autoimmune disorders such as psoriasis [28]. In this skin disease, TNF provokes signals and transcripts via the Janus kinase pathway, JAK-STATs (signal transducers and activators of transcription) and NF-κB, producing cytokines that mediate inflammation [29]. On the other hand, MCs produce IL-10 which inhibits hypersensitivity reactions and skin responses to ultraviolet irradiation, dampening inflammation [30]. In addition, MCs produce IL-33 (and are activated by it), which is expressed by skin keratinocytes and endothelial cells and amplifies the inflammatory process [26]. IL-36 is also expressed in skin and acts as an autocrine cytokine on skin resident fibroblasts, MCs and keratinocytes [31]. The proinflammatory network of cytokines involving MCs in the skin include, as key mediators, IL-33 and IL-36; therefore, inhibiting IL-36 with IL-38 could alleviate the inflammatory state exerted by MCs [32]. In contrast, MCs also perform a protective function of the skin against bacterial infections, by producing some cytokines such as IL-6 that contributes to the

killing of infectious bacteria [33]. IL-36 was discovered in 1999 and is a member of the IL-1 family [34]. This family comprises 11 proteins, of which seven with agonistic activity: IL-1 alpha, IL-1 beta, IL-18, IL-33, IL-36 alpha, IL-36 beta and IL-36 gamma, three IL-1Ra, IL36Ra, and IL-38 receptor antagonists, and one anti-inflammatory cytokine, IL-37, which translocates to the nucleus, and suppresses the transcription of proinflammatory genes [35]. Moreover, IL-37 is secreted intracellularly, where it binds the receptor IL-18Ra, recruits the TIR8 signal and suppresses NF- κ B and MAPK with consequent inhibition of inflammation [36]. IL-36 binds to its receptor, called IL-36Ra (IL-36 receptor antagonist), which binds IL-36R (also called IL-1R6) but does not recruit the co-receptor and, consequently, does not transmit the signal [37]. IL-36Ra inhibits the activation of IL-36 receptor IL-36R signaling pathway, exerting an anti-inflammatory action [38]. All subtypes of IL-36 have a molecular weight about 18 KDa that binds to the same receptor, also formerly called IL-1RL2 or IL-1Rrp2 [39]. IL-36 intervenes in both innate and adaptive immunity. This cytokine activates the MAPK and NF- κ B pathway and induces the production of proinflammatory cytokines [40]. The binding of IL-36 to its own receptor and to the IL-RAcP co-receptor leads to transduction of the NF- κ B signal, or MAPK activation [38]. IL-36 is expressed by macrophage, CD4⁺ T cells, dendritic cells and other cells [38]. IL-36Ra shares 52% of homology with IL-1Ra, another cytokine inhibitor of the IL-1 family [31]. IL-36 contributes to the maturation of dendritic cells by stimulating the secretion of IL-12 which participates in the differentiation of T-cells in Th1 cells [41]. In addition, IL-36 plays a critical role on Th1 response and is expressed on the skin as a pro-inflammatory cytokine in psoriasis [42]. This cytokine has biological activity including its inflammatory properties on the skin where it is expressed abundantly by keratinocytes [43]. In the psoriatic skin, IL-36 is related to Th1 and Th17 cytokines and mediates various autoimmune inflammatory diseases, such as systemic lupus erythematosus, inflammatory bowel disease, ulcerative colitis, Crohn's disease and psoriatic arthritis, as well as inflammation of the tissues induced by microbial infections [44]. Therefore, skin gamma-delta T cells, Th1 and Th17, produce IL-36 which plays a key role in the pathogenesis of psoriasis. In *in vivo* experiments, transgenic

mice expressing a high amount of IL-36 in cutaneous keratinocytes show skin lesions similar to psoriasis, demonstrating the importance of this proinflammatory cytokine [45]. In addition, stimulation of IL-36 can also induce a high production of other proinflammatory cytokines, such as IL-6, IL-8, TNF and a number of chemokines [46, 47]. Chemokines are chemoattractant cytokines of leukocyte trafficking to sites of inflammation, though their biological role is not limited to chemotaxis since they present many biological effects [48]. In fact, chemokines are involved in hematopoiesis, innate and acquired immunity, angiogenesis and metastases [49]. In *in vitro* study, MCs stimulated by SP and treated with IL-37 [50, 51], a cytokine with properties similar to those of IL-38, do not inhibit chemokines CC5 or CXCL8 (which attract mononuclear cells and neutrophils, respectively) (unpublished data), while, IL-38 does. Suppressing IL-36, for example with IL-38 binding IL-36R, would mean providing safe relief to the patients with chronic proinflammatory diseases including psoriasis. To date, many treatments for psoriasis have been proposed, such as bone marrow transplantation, corticosteroid treatment or anti-TNF therapy, but all still need to be improved, although some antibodies, such as anti-IL-17, anti-IL-17 receptor, anti-IL-12/23p40, and anti-IL-23p19, have dramatically changed the treatment of psoriasis. Furthermore, studies on transgenic mice have provided valuable information on the pathogenesis of this disease. Thus, here, we propose new therapy with the hope that it will have an effective impact on psoriasis, chronic proinflammatory disease [52].

IL-33 pro-inflammatory or anti-inflammatory

IL-33 also called “alarmin” is one of the danger-associated molecular patterns (DAMPs) molecules, also known as endogenous danger signals, with properties to mediate sterile inflammatory responses due to trauma, without the intervention of microorganisms [53]. IL-33 can be released from MCs after physiological stress as occurs in psoriasis, a non-allergic hyper-proliferative inflammatory skin disease with an important neurogenic component. MCs through the production of IL-33 intervenes in metabolic homeostasis and in various diseases of the central nervous system including stress that exacerbates psoriasis [54]. In recent years, it has been seen that IL-33 in

addition to being involved in the activation of MCs is also able to stimulate type 2 innate lymphoid cells (ILC2s), Tregs, natural killer cells and CD8 + T lymphocytes [55]. IL-33 possesses pleiotropic activity in immune responses and through its ST2 receptor activates the JNK signaling pathway demonstrating that by manipulating the ST2/IL-33 ratio one could have a better understanding of inflammatory mechanisms. IL-33 is localized in the cell nucleus and by binding to p65 of NF- κ B it can also have an inhibitory action on the transcription activity of NF- κ B, in fact, IL-33 in regulating Th2 cells has a contrast to pro-inflammatory IL-18 [53]. In psoriasis can be an augmentation of neurotransmitters such as substance P (SP) which induces VEGF in human mast cells, an effect that leads to increased IL-33 and inflammation [1]. IL-33 which is released from MCs without cleavage by caspase 1, is a critical player of immune response to tissue suffering and acts through its ST2 receptor, a member of the IL-1 family, located in the human chromosome 2 locus, implicated in T helper 2 (Th2) responses in MCs-driven allergic diseases. About 10 years ago, our group reported that the neurotransmitter SP induces gene expression and VEGF secretion in human umbilical cord blood-derived cultured mast cells (hCBMCs) an increased effect with IL-33 administration, involving the PKC pathway and the MAPK ERK and JNK. These results demonstrate that IL-33 intervenes in inflammatory conditions including psoriasis, where neurotransmitters can aggravate inflammation. In addition, we have shown that IL-33 administered in combination with SP strongly increases the gene expression of TNF in human mast cells in vitro, an effect that would also occur in psoriasis mediated by neurotransmitters. The activation of MCs by IL-33 causes the release of histamine and cytokines / chemokines which are very important in rheumatic diseases including psoriasis, as on the one hand it can increase the inflammatory process; while on the other it can inhibit the macrophage response.

Therefore, taken together all these concepts expressed herein demonstrate that IL-33 can exacerbate inflammatory allergic skin reaction (“alarmin”) and increase TH1 response, as occurs in experimental arthritis induced in mice; but also IL-33 is capable of inhibiting pro-inflammatory IL-

18 released by macrophages, demonstrating an anti-inflammatory activity. However, these data are still under study and remain to be clarified.

IL-1 and psoriasis

Psoriasis is characterized by the activation of MCs, proliferation of keratinocytes, production of IL-1 and is result of inflammation [56]. Psoriasis is also activated and/or exacerbated by stress with the release of pro-inflammatory neurotransmitters that activate MCs in inflammation. In addition, IL-1 can be induced by ultraviolet B (UVB) radiation on skin cells, including keratinocytes.

About 35 years ago our group pointed out that IL-1 plays an important role in the pathogenesis of many immunological, inflammatory, infectious and neoplastic diseases [57]. Today, the role of IL-1 has been sufficiently well defined and it has been shown that this cytokine is strongly linked to inflammation, as a primary function, but also to cellular resistance to infections and foreign antigens [57].

The IL-1 family has 11 cytokine members and 10 receptors, all participating in both immunological and inflammatory responses [58]. IL-1 is a polypeptide whose genes can be activated by various inflammatory perturbations in any tissue or organ, causing the stimulation of a number of cells including MCs. The release of allergic mediators from MCs is affected by IL-1 and other cytokines. Immune cells, such as macrophages and granulocytes activated by IL-1, can release arachidonic acid metabolites and synthesize proteases, as occurs in PGD₂ released by MCs,. Furthermore, it has been reported that pro-IL-1, mature IL-1 and TNF can cause a release of histamine from basophilic cells, an effect correlated with the anti-IgE response [59]. Allergens in the skin can activate MCs, which cause the release of acute phase proteins and cytokines, which can be also synthesized by other activated immune cells, consequently causing intense inflammation. In psoriasis, high levels of histamine can occur during both the acute and late phases, but also the levels of tryptase and PGD₂ can be higher. In light of these data, it is pertinent to think that preventing the generation of

IL-1 through the blockade of its receptor (IL-1Ra) can have an effective therapeutic response for both psoriasis and other inflammatory diseases.

IL-1 receptor antagonist in psoriasis

MCs are effector cells in many biological responses, providing an important biological function involving many organs including the skin [60]. Among the skin diseases, we find psoriasis, which is a chronic relapsing inflammatory disease with several symptoms including itching and an immune imbalance.

The disease presents clinical points mediated by inflammatory cytokines including IL-1, which plays an important pro-inflammatory role through its IL-1R1 receptor [38]. IL-1 receptor is expressed in almost all tissues and its activation causes inflammation; therefore, by blocking this receptor, a therapeutic effect can be obtained in inflammatory diseases mediated by IL-1.

IL-1Ra is found in the bloodstream of healthy subjects at a concentration ranging from 100 to 300 ng/ml and it is a natural molecule of the IL-1 family, most currently used for the treatment of rheumatoid arthritis, but has also been shown to be effective in a broad spectrum of inflammatory diseases including stroke and some autoimmune diseases [61]. Serum levels of IL-1Ra are high in many inflammatory and autoimmune diseases, including psoriasis, an effect due to the body's response to inflammatory stimuli. The IL-1 genes and their proximity to IL-1Ra indicate that these two cytokines are very similar and have the same origin. IL-1Ra binds, at high affinity, to the IL-1R receptor without inducing IL-1RAcP co-receptor, and therefore does not cause any change, but it performs an antagonist action by competing with IL-1. IL-1Ra has an anti-inflammatory action that limits the production of IL-1 in rheumatoid arthritis and psoriatic conditions, although this inhibition does not completely resolve the pathological clinical signs.

As reported above, IL-1 stimulates the production of IL-6 in MCs, a specific effect without the implication of degranulation. IL-1Ra can be highlighted in neurological diseases where IL-1 in stimulating the production of IL-6 increases the inflammatory process but can be also

neuroprotective. IL-1Ra administration in rodents has been reported to cross the blood-brain barrier reducing inflammatory neurological diseases [62]. As IL-1 is implicated in clinical inflammatory brain manifestations, targeting IL-1 can cure related symptoms, including those caused by stress that can exacerbate inflammation in psoriasis.

In inflammatory processes, including psoriasis, IL-1Ra can inhibit inflammation by reducing granulocyte infiltration and release of protease, IL-6 and fibrinogen, lowering CRP levels [63]. Treatment with IL-1Ra in arthritis improves pain and itching, and has beneficial effects with therapeutic results that can also occur in other conditions including fever, arthralgia, fatigue, rash and other symptoms related to inflammation [64]. Today, hundreds of thousands of patients worldwide with autoimmune diseases, including psoriasis, are treated with anti-inflammatory cytokines that inhibit IL-1; although a small percentage of those treated may develop bacterial infections. Several data report that IL-1Ra not only relieves the stress caused by IL-1, which aggravates the psychiatric state, but also limits fever and shock, pathological conditions that can affect the health of patients. IL-1Ra deficiency can develop inflammatory diseases such as arthritis and psoriasis. In *in vivo* model, rodents with low levels of IL-1Ra can develop a psoriasis-like rash, arthritis and other diseases related to immunodeficiency such as tumors and infections with skin pustules and vasculitis [65]. Endothelial cells of the dermis express IL-1R which after antigen activation releases IL-1. This potent cytokine stimulates nearby MCs to produce TNF which has an inflammatory effect and stimulates endothelial cells to produce other pro-inflammatory compounds such as chemokines CXCL8, CCL20, CXCL1 and cytokine IL-6 [66]. In addition, expression of adhesion molecules including ICAM-1 (intracellular adhesion molecule) and V-CAM (vascular cell adhesion molecule) can occur in the site of psoriatic inflammation, causing an increase in the number of T cells in loco, which also participate in the inflammatory network. All these effects can certainly increase the inflammatory state in psoriasis. Using IL-1Ra, the above-mentioned effects can be reduced through IL-1 blocking and thus inhibition of inflammation. The satisfactory clinical

results of IL-1Ra led to the development of the drug Anakinra which has been approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis.

In conclusion, this article focused on the contribution of MCs and their secreted and released products in psoriatic inflammation, demonstrating that these cells are very important in aggravating the disease, a process that can be limited with the use of new anti-inflammatory cytokines such as the IL-37, IL-38, or IL-1Ra. However, to verify these effects, to improve them and ascertain their validity, further experiments are needed in the future.

IL-38: inhibitory effect

It has been recently reported that IL-38 plays key role in many inflammatory disorders, including asthma, rheumatoid arthritis, and atherosclerosis [67]. IL-38 (or IL-1F10), the last cytokine member of the IL-1 family, was discovered in 2001 [52]. IL-38 binds to IL-36R6 (IL-36 receptor 6) causing anti-inflammatory activity by reducing several cytokines, including IL-1, IL-6 and IL-8, in experimental inflammatory diseases [68] (Fig. 2). IL-1 family, includes two receptors antagonists (IL1Ra and IL-36Ra), two cytokines that suppress inflammation (IL-37 and IL-38) and seven pro-inflammatory cytokines, including IL-1 and IL-33. IL-38, also referred to as IL-1F10, is similar to the IL-1 receptor antagonist (IL-1Ra) and to the IL-36 receptor antagonist (IL-36Ra). IL-38 is expressed in many cells but in particular in epithelial cells, B cells and tonsils, all elements of defense against external invaders [68]. The cellular receptor of IL-36 specifically binds IL-38 and does not bind to IL1R1, IL-1R3 or IL-18R α . By binding IL-36 receptor, IL-38 inhibits human mononuclear cells stimulated with IL-36 *in vitro*, an effect shared with IL-36Ra, which it resembles for its inhibitory effects, in particular on the Th-17 response [69]. In addition, human IL-38 inhibits the production of pro-inflammatory IL-17 and IL-22 by human peripheral blood mononuclear cells (PBMC) *in vitro* [67]. In IL-38-deficient mice, Th17 response is increased along with inflammation. In psoriasis, as well as other autoimmune inflammatory diseases, IL-17 plays a role as a very important cytokine in the inflammatory process, and is a crucial key in the pathogenesis of various chronic proinflammatory diseases [69]. Therefore, IL-17, which strongly induces IL-36 in psoriasis,

is a target molecule for the study of new therapies in autoimmune disorders. It should be emphasized that this inhibitory effect of IL-38 on IL-36 receptor is almost always partial and with different effects, as it depends on the cells or tissues examined. The cytokine IL-38 generates new hope in the treatment of diseases difficult to cure such as chronic proinflammatory diseases, mediated by inflammatory cytokines of the IL-1 family.

The inhibition of inflammatory members of the IL-1 family has attracted much attention from researchers for the treatment of various inflammatory diseases including psoriasis. Thus, here we confirm that IL-38 cytokine emerges as an inhibitor of inflammation and is an important suppressor molecule and interesting marker in diseases [70]. However, the power of the anti-inflammatory effect of IL-38 still has some dark points, since the binding to its receptor is quite weak and the effective concentration of this cytokine in humans is still unknown. Therefore, IL-38 holds promise of innovative therapeutic tools, but more in-depth studies are needed to establish the true biological value of this interesting novel cytokine.

Inhibitory effect of IL-37

MCs are activated during allergic and anaphylactic reactions by mediating innate and acquired immunity, but these cells can also be activated by non-allergic triggers such as neuropeptides and cytokines, as occurs in certain neurological diseases [71]. In fact, IL-1 has the ability to stimulate MCs to produce IL-6 TNF and IL-33 without degranulating, building a powerful pro-inflammatory network, an effect that increases with stress, which exacerbates psoriasis. Therefore, targeting IL-1 could represent a very significant tool to inhibit inflammation. IL-37 is an important suppressor of innate immune cells that can lead to new potential therapeutic approach and application. IL-37 is a member of the IL-1 gene family that broadly inhibits inflammation in various inflammatory and autoimmune diseases, while also reducing acquired immunity, paving the way for a healing effect of psoriasis [72]. In fact, the dendritic cells (DC) that express IL-37 are tolerogenic, an effect which reverberates on the activation of the responses of effector T cells, inducing Treg cells and inhibiting

the adaptive immunity [73]. In rodent experiments, IL-37 has shown protection in many induced inflammatory pathologies, while also suppressing the immune response [74]. This new innate cytokine inhibitor, non-specifically reduces several inflammatory cytokines and chemokines in autoimmune rheumatic diseases by acting on the suppression of mTor and increasing the activity of AMP kinase [75]. Therefore, administration of recombinant human IL-37 to rodents reduces inflammatory metabolism and increases oxidative phosphorylation by acting both at a systemic and local tissue level, including skin. IL-37 inhibits IL-1 β , IL-6, and TNF cytokines, which play a fundamental role in psoriatic inflammation, but it can also suppress some chemokines such as CCL2, which is also important in psoriasis and rheumatic diseases [76]. Levels of the IL-37 protein and its mRNA are lower in healthy rodents, while individuals deficient in IL-37 may be more prone to inflammatory pathologies [77]. In fact, this cytokine was found to be higher in some rheumatic diseases including psoriasis, showing that the body produces IL-37 as a response to excessive inflammation (Fig. 3) [78]. This demonstrates clearly that IL-37 is involved in rheumatic diseases and psoriasis and could certainly play a role in the treatment of these complex pathologies [79]. This article shows for the first time how IL-38 and IL-37 may represent a new potential anti-inflammatory therapeutic pathway in psoriasis and probably other skin diseases mediated by IL-1 family members. Therefore, IL-37 and IL-38 hold promise of innovative therapeutic tools [80], but more in-depth studies are needed to establish the true biological value of these interesting novel cytokines.

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FIGURE LEGENDS

Fig. 1. Generation of proinflammatory cytokines by IL-1, IL-33 and TNF from activated mast cell (biochemical pathway), and release of tryptase and TNF by degranulation.

Fig. 2. Keratinocyte and mast cell secrete proinflammatory cytokines IL-1 and IL-33 which activate macrophage to generate IL-36. Inhibitory effect of IL-38 through the IL-36 receptor binding leads to inhibition of inflammation in psoriasis.

Fig. 3. Synthesis and production of IL-37 via TLR, production of mRNA, and pro-IL-37 which, through caspase-1, leads to the mature form of IL-37 that translocates to the cell nucleus.