

Potential therapeutic use of IL-37: a key suppressor of innate immunity and allergic immune responses mediated by mast cells

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Abstract The host response to either exogenous or endogenous insults produces a series of changes, characterized by alterations in immunological functions and generation of mediators called cytokines which include the interleukin-1 (IL-1) family members. IL-1 acts as a hormone mediating the host responses to infection and inflammation. Blocking inflammatory IL-1 family members can be effective against inflammatory disorders, including allergies. IL-37, (formerly IL-1 family member 7), emerges as an inhibitor of innate and adaptive immunity by reducing circulating and organ cytokine levels. IL-37, mainly expressed in dendritic cells, monocytes, and plasma cells after TIR ligand activation, inhibits inflammatory cytokines and augments the level of anti-inflammatory IL-10.

All the authors contributed equally to the conception and design of this review and the analysis and interpretation of data, as well as revising and approving the final version.

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IL-37 is involved in allergic reaction and its expression in dendritic cells causes tolerogenicity and inhibits inflammatory response. Mast cells (MCs) are ubiquitous in the body, reside in numerous mucosal tissues, and are mediators of allergic reaction, and innate and adaptive immunity. MCs are important regulators of cytokine generation in the course of inflammatory responses and allergy, and are implicated in the pathophysiology of allergic asthma. Cysteine protease caspase-1 activation leads to the cleavage of pro-form of IL-1 into active mature IL-1 which is present in stimulated and unstimulated inflammatory MCs. Inflammatory cytokine inhibition, along with the augmentation of anti-inflammatory IL-10 by IL-37, is certainly beneficial and improves the pathogenesis of allergic disorders. However, in these studies, the exact mechanism(s) of IL-37-induced anti-inflammatory and anti-allergic activity along with its side effect(s) remain to be determined.

Keywords Allergy · IL-37 · Inflammation · Immune response · Mast cells

Introduction

Over 30 years ago, we published that the cytokine IL-1 family plays an important role in the pathogenesis of many diseases and functions with a wide range of biological activities, furthermore it is clearly an important mediator of host response to various infectious, inflammatory, neoplastic, and immunologic challenges [1].

In recent years, data has accumulated to support the idea that pro-inflammatory cytokines contribute to the development and progression of many immunological and inflammatory diseases [2, 3]. Cytokines are pro-inflammatory and anti-inflammatory proteins that elicit

their effects in an autocrine and paracrine manner [4, 5]. A number of pro-inflammatory and anti-inflammatory mediators have been detected in allergic and inflammatory disorders, and the balance between these opposing cytokine activities regulates disease severity [6–10]. Therefore, cytokines are active in inflammatory diseases, and inhibiting these protein mediators with antagonists (such as monoclonal antibodies, soluble receptors, certain cytokines, and receptor antagonists) results in a therapeutic action [11, 12].

Many laboratory and clinical data indicate the efficacy of the various anti-cytokine treatments in the therapy of inflammation and allergic diseases [13, 14].

The existence of anti-inflammatory cytokines, such as (TGF)- β , IL-10, IL-4, and IL-1 receptor antagonist (IL-1RA), opens up new therapeutic pathways against immune diseases, autoimmunity, and inflammation. The modulation of cytokines plays an important role in regulating inflammatory diseases and may be implicated in therapeutic processes [15, 16].

Anti-inflammatory cytokines are involved in diverse signaling pathways and inflammatory diseases including neuro-inflammation, allergic diseases, and asthma. It is well known that anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13, play an important role in the pathogenesis of allergic asthma, even if the full mechanism remains unclear [17].

In the present article, the most relevant biological effects of IL-37, a new immunological protein, are reviewed, focusing on its anti-inflammatory and anti-allergic actions, which are promising therapeutical compounds.

In this review, the anti-inflammatory effect of IL-37 in the light of new findings was studied.

IL-37 (formerly IL-1 family member 7) which originates from hematopoietic cells is a new cytokine naturally expressed in several cells and described as a negative regulator of immunity and inflammation [18]. IL-37 (molecular weight circa 45 kDa) includes different variants, namely, IL-1F7a, b, c, d, which bind IL-18 receptor α -chain but do not act as a receptor antagonist [19]. Among these proteins, IL-37b is the largest which is cleaved by caspase-1 from IL-37 precursor into mature IL-37 (Fig. 1). Caspase-1 is a cysteine protease, which transmits the signals via G protein-coupled receptors. Caspase activation also leads to cleave IL-1 precursor into active mature IL-1 (“alarmin”). After activation, several cell types, such as peripheral blood mononuclear cells (PBMC), monocytes, plasma cells, dendritic cells, epithelial cells, carcinoma cells, and organs (testis, thymus and uterus) generate IL-37 mRNA and/or IL-37 protein [20] (Fig. 1).

Through an intracellular mechanism translocating to the nucleus, this cytokine exerts several biological functions [20, 21]. Endogenous IL-37 is mainly produced by macrophages which increase upon stimulation with LPS and/or different toll-like receptor (TLR) ligands and is expressed in inflamed and allergic tissues and in a minor quantity in healthy and physiological states [22].

IL-37 abrogates pro-inflammatory cytokines in activated immune cells, such as macrophages and mast cells, inhibiting intracellular and extracellular immune responses, inflammation, and allergy [23].

Activated antigen-presenting cells (APC) are almost totally inhibited by IL-37 in their generation of pro-inflammatory cytokines, while anti-inflammatory cytokines are uninhibited. Therefore, IL-37 is a negative regulator of innate and adaptive immunity [24] (Fig. 2).

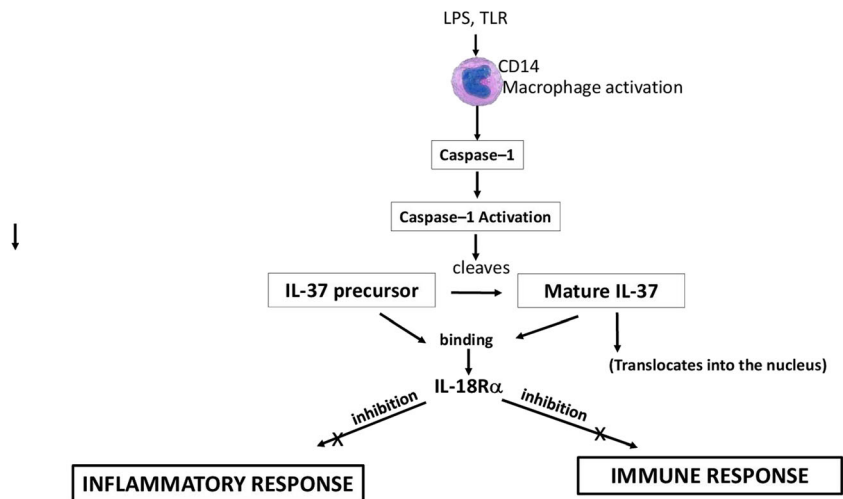
Moreover, IL-37 strongly inhibits the expression of IL-1 α , IL-1 β , TNF, IL-23, IL-17, IL-18, and IFN- γ , and in human monocytes, reduces IL-1 β -induced expression of IL-1 α , IL-6, TNF [22], and certain chemokines including MIP-2/CXCL2, MCP-5/CCL12, BCA-1/CXCL13, and IL-8 in many different cell types [25].

Recent research has highlighted that IL-37, binding IL-18R α , plays an important role in allergic reactions, including asthma [23] (Fig. 3). After antigen stimulation, administration of IL-37 leads to an inhibitory effect of hyper-responsiveness, reduction of mucus production, and pro-inflammatory cytokine generation, suggesting that IL-37 is a critical and potential target in allergic reactions [23]. Allergic diseases involve multiple cell types of innate and adaptive immunity, including macrophages, neutrophils, Th2 cells, basophils, eosinophils, airway epithelial cells, natural killer T cells, Tregs, Th17, dendritic cells, bronchial epithelial cells, and mast cells [26–28].

IL-1, mainly generated by APC, serves a role in host defense to pathogens and triggers inflammatory responses by multiple mechanisms but also serves as local amplifier of innate and adaptive immunity. Dysregulation of IL-1 expression may lead to the development of several autoimmune disorders and has a potential pathogenic role in IL-1R signaling. IL-1R-blocking agents are certainly useful for treating inflammatory diseases [4].

Mast cells (MCs) are ubiquitous in the body and are immune effector cells involved in allergic immune responses and inflammation [29–31]. As is well known, MCs respond to allergens, inducing inflammation and leading to the production of several cytokines [32, 33]. MCs are found within tissues surrounded by immune cells producing inflammatory cytokines and are present in the pathogenesis of patients with allergy [4, 34]. Cytokines are necessary for mast cell maturation, since human cord blood CD34+ cells differentiate and grow into MCs in the presence of stem cell factor (SCF) and interleukin (IL-6) [9]. IL-6 secreted by Th2 cells or mast cells binds to its receptor IL-6R α (gp 80). IL-6 is a pleiotropic cytokine (26 kDa) produced in many diseases, which upregulates MC histamine production and is an important inducing factor for the expression of Fc ϵ RI receptor. MCs participate in human innate and adaptive immune responses and express on their surface *c-kit* receptor, SCF, and the high-affinity receptor ($K_d = 10^{-10}$ M) Fc ϵ RI for immunoglobulin E (IgE) [2]. Cross-linking of bound IgE by antigen activates

Fig. 1 Macrophage activation by LPS leading to caspase-1 activation and therefore production of secretion of IL-1 pro-inflammatory family members, including IL-37 which binds IL-18R α and provokes inhibition of immune response and allergic inflammation



protein tyrosine kinases, such as *Syk* and *Lyn*, in turn triggering activation of a mitogen-activated protein (MAP) kinase cascade and a phosphatidylinositol-specific phospholipase C (PI-PLC γ) [3]. MAP kinase acts on the MC nucleus and activates cytokine gene expression with generation of inflammatory cytokines. Activation, migration, and maturation of MCs are regulated by cytokines, such as TNF, IL-1 family members (e.g., IL-1 β , IL-18, and IL-33), TGF- β , nerve growth factor, IL-3, IL-9, and CXCL12, also involved in allergic inflammation. IL-37 may be an intracellular regulator which modulates

the signaling events initiated by Fc ϵ RI or other activating receptors such as TLR-9 and TLR-3 and c-kit. IL-37 reduces cJun and p38 MAPK phosphorylation, pro-inflammatory signals STAT transcription factors, and p53, affecting cellular proliferation and differentiation [3] (Fig. 2).

Indeed, IL-37 treatment of allergic reaction has been reported to inhibit a number of pro-inflammatory mediators including M-CSF, GM-CSF produced by activated dendritic cells and TNF, IL-1, IL-18, and IL-33, which display an important function in host defense, immune regulation,

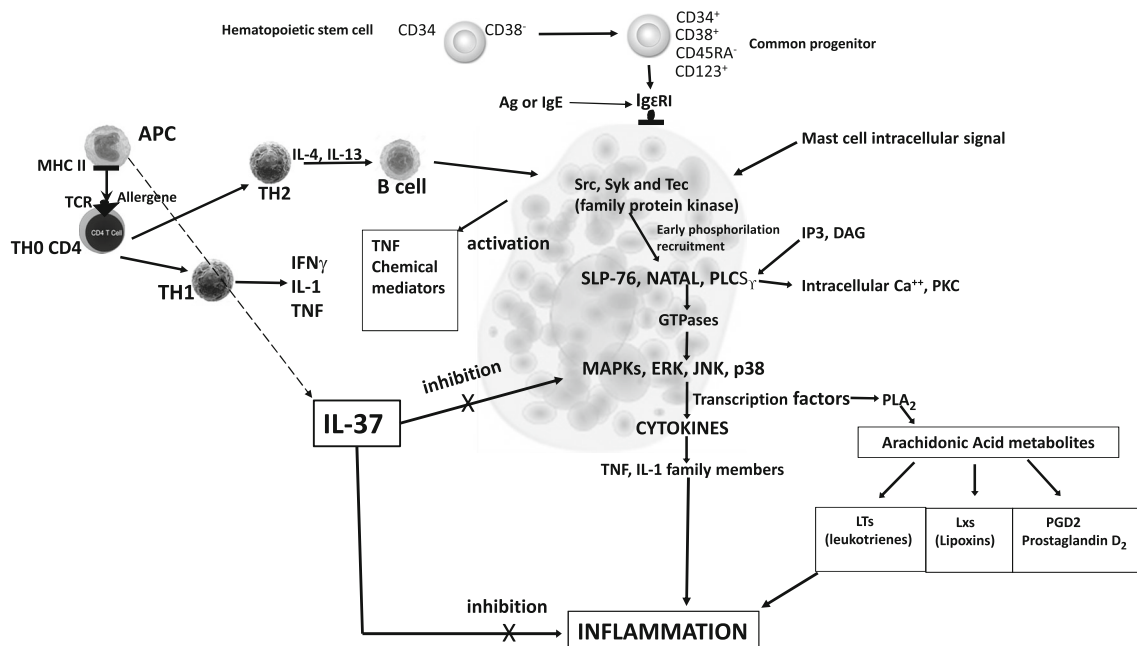


Fig. 2 Mast cell generation from hematopoietic stem cells activated by antigen leads to cytokine transcription and translation, inducing inflammation which is inhibited by IL-37 generated by activated macrophages and Th1 cells. In addition, inflammation can be amplified by arachidonic acid cascade products. Abbreviations: *IL* interleukin, *LPS* lipopolysaccharide, *TLR* toll-like receptor, *PLA* phospholipase A, *PLC* phospholipase C, *Src* proto-oncogene

tyrosine-protein kinase *Src*, *Syk* spleen tyrosine kinase, *Tec* tyrosine kinase expressed in hepatocellular carcinoma, *SLP-76* Src homology 2 domain-containing leukocyte phosphoprotein of 76 kDa, *NATAL* non-T cell activation linker, *PKC* protein kinase C, *IP3* inositol 1,4,5-trisphosphate, *DAG* diacylglycerol, *MAPK* mitogen-activated protein kinase, *ERK* extracellular signal-regulated kinase, *JNK* c-jun N-terminal kinase, *p38* protein 38

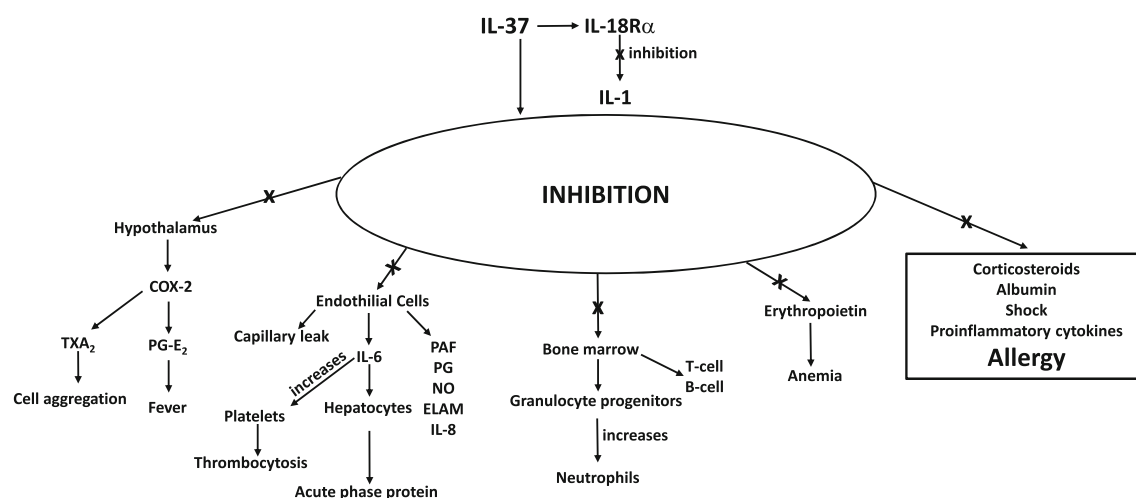


Fig. 3 IL-37 binding IL-18R α inhibits several inflammatory pathways including allergy, acute phase protein, and other pathological inflammatory diseases

inflammation, and allergy [35]. IL-37 may also inhibit TNF and IL-1 released by LPS mast cell activation, *in vitro* [35].

In allergic inflammation, Th2 cytokines are released, and eosinophils and MCs along with smooth muscle cells and epithelial cells secrete VEGF which is influenced by many other inflammatory pathways, and may be also inhibited by IL-37 [36].

Therefore, IL-37 is a key cytokine in regulating the allergic and immunological responses, mainly by inhibiting the expression, production, and function of pro-inflammatory cytokines such as IL-1, and IL-33 generated by MCs [3]. However, in some cases, it has been reported that even the anti-inflammatory cytokines IL-13, IL-10, and I-309 are inhibited by IL-37 [37].

IL-37 may downregulate the transcription and translation of several cytokines including IL-33 which plays a role in allergic reactions through mast cell activation and is elevated in atopic patients during anaphylactic shock [38]. IL-37-blocking IL-33 leads to an inhibitory effect of innate immunity-mediated splenomegaly, blood eosinophilia, pulmonary inflammation, epithelial hyperplasia, and massive mucus production in the lungs and stomach [39]. IL-37 helps to reduce the severity of disease, demonstrating the important role of inflammatory cytokines in allergic disorders [35].

By suppressing the immune responses, IL-37 has a potential role in autoimmunity, transplantation, and allergy; however, its suppression on inflammatory cytokines is undesirable under physiological conditions since it modifies the innate immune responses [24].

The study of the mechanisms of allergic reactions is poorly understood and the inhibitory effect of IL-37 in allergy, mediated by MCs and cytokine generation, is an emerging field and still in the early stages of development.

Cytokines generated from MCs regulate the inflammatory response, but the exact mechanism by which they regulate distinct features of the allergic reactions is still unknown. The effect of IL-37 makes this cytokine an attractive target for the inhibition of mast cell-mediated allergy and may contribute to the beneficial effects of immunotherapy. The fact that IL-37 inhibits mast cell mediating allergy and inflammation greatly expands our understanding of the development of allergy.

In conclusion, MCs contribute to allergic reactions inhibited by IL-37 and this phenomenon may have a therapeutic potential; however, these studies clearly require additional research, since the current data in the field are insufficient and the full mechanism(s) by which this cytokine elicits the anti-inflammatory responses is not totally understood [40]. However, more studies are required to precisely define the specific role of IL-37 on MCs mediating allergy. For this reason, experiments using anti-inflammatory cytokine IL-37 are in progress in our laboratories.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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