Cytokine and Growth Factor Reviews 49 (2019) 32–41

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Insight into interleukin-37: The potential therapeutic target in allergic diseases

Zhaohao Huang[a,1], Lihui Xie[a,1], He Li[a], Xiuxing Liu[a], Joseph A. Bellanti[b], Song Guo Zheng[c,*], Wenru Su[a,*]

[a] State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China
[b] International Center for Interdisciplinary Studies of Immunology (ICISI), Georgetown University Medical Center, Washington, DC 20057, United States
[c] Department of Internal Medicine, Ohio State University College of Medicine, Columbus 43210, OH, United States

ARTICLE INFO

Keywords:
Allergic diseases
Anti-inflammatory effect
Hypersensitivity
Inflammation
Interleukin-37

ABSTRACT

Allergic diseases are ubiquitous diseases with detrimental effects on the quality of life of people worldwide. Common allergic diseases include asthma, allergic rhinitis (AR) and allergic dermatitis (AD). Recently, studies have shown that interleukin (IL)-37, a novel cytokine in the IL-1 family, exhibits broad protective properties in various diseases, such as autoimmune diseases and cancer. IL-37 displays its anti-inflammatory effect on diseases by curbing innate and acquired immunity as well as inflammatory reactions. IL-37 functions by forming a complex with IL-18Rα and IL-1R8 extracellularly and can be translocated to the nucleus upon forming a complex with mothers against decapentaplegic homolog 3 (Smad3) intracellularly, thereby affecting gene transcription and signaling pathway activation. In addition, increasing evidence confirms that IL-37 expression is aberrant in asthma, AR and AD, which indicates that IL-37 may also play essential roles in allergic diseases. Furthermore, accumulating data obtained from recombinant IL-37 (rIL-37)-treated mice and from IL-37 transgenic (IL-37tg) mice suggest a protective role for IL-37. This review will detail the role of IL-37 in the occurrence and development of allergic diseases and discuss the potential of IL-37 as a therapeutic target in allergic diseases.

1. Introduction

In the past few decades, the morbidity of allergic diseases has dramatically increased worldwide and has become a major public health issue [1]. Allergic diseases not only cause physical and psychological damage to patients' health but also impose a large socioeconomic burden [2]. Allergic diseases involve several diseases resulting from immune system hypersensitivity to specific substances in the environment [3]. Asthma, allergic rhinitis (AR) and allergic dermatitis (AD) are common allergic disorders in people [4,5]. An increasing understanding of allergic diseases has helped to recognize the central role of the interleukin (IL) family in the occurrence and development of allergic diseases [6,7].

IL-37, a novel member of the IL-1 family, extensively curbs innate and acquired immunity [8,9]. The broad anti-inflammatory signature of IL-37 was initially demonstrated by Charles A Dinarello, who found that

Abbreviations: AR, allergic rhinitis; AD, allergic dermatitis; IL-37, interleukin-37; rIL-37, recombinant interleukin-37; IL-37tg, interleukin-37 transgenic; Smad3, mothers against decapentaplegic homolog 3; FIL1ξ, family of interleukin-1ξ; IL-1H4, interleukin-1 homologues 4; IL-1RP1, interleukin-1-related protein 1; IL-1H, interleukin-1 homologues; IL-1F7, interleukin-1 family member 7; LPS, lipopolysaccharide; PBMCs, peripheral blood mononuclear cells; DCs, dendritic cells; TLR, toll-like receptor; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor α; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; TGF-β, transforming growth factor beta; IL-18Rα, interleukin-18 receptor α; IL-1R8, interleukin-1 receptor 8; TIR, toll/IL-1 receptor; SIGIRR, single Ig IL-1R-related molecule; IL-18BP, interleukin-18 Binding Protein; ERK, extracellular signal-regulated kinase; p38MAPK, p38 mitogen-associated protein kinase; JNK, c-Jun N-terminal kinase; PI3K, phosphatidylinositide 3-kinases; AKT, protein kinase B; mTOR, The mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; TAK1, transforming growth factor beta-activated kinase; STAT, signal transducers and activators of transcription; PTEN, phosphatase and tensin homolog deleted on chromosome ten; GM-CSF, granulocyte-macrophage colony stimulating factor; ICAM-1, intercellular cell adhesion molecule-1; BMDMs, bone marrow-derived macrophages; HDM, house dust mite; AHR, airway hyperreactivity; TH2, T helper 2; OVA, ovalbumin; BALF, bronchoalveolar lavage fluid; ILC, innate immune cells; ASMC, airway smooth muscle cells; TEC, tracheobronchial epithelial cells; AEC, alveolar epithelial cells; TSLP, thymic stromal lymphopoietin; ECP, Eosinophil Cationic Protein; Treg, regulatory T cells; ACD, allergic contact dermatitis; CHS, contact hypersensitivity

* Corresponding authors.
E-mail addresses: SongGuo.Zheng@osumc.edu, songguozheng2013@yahoo.com (S.G. Zheng), suwr3@mail.sysu.edu.cn (W. Su).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cytogfr.2019.10.003
Received 20 September 2019; Accepted 10 October 2019
Available online 18 October 2019
1359-6101/

Table 1
Human IL37 transcripts and IL-37 isoforms.

Isoform	Exon1	Exon2	Exon3	Exon4	Exon5	Exon6	Residues
IL-37a			√	√	√	√	192
IL-37b	√	√		√	√	√	218
IL-37c	√	√			√	√	178
IL-37d	√			√	√	√	197
IL-37e	√				√	√	157

IL-37 could curb immune responses by keeping the cytokine balance away from excessive inflammation [10]. Emerging studies have indicated the pivotal role of IL-37 in limiting excessive inflammatory responses as well as avoiding rampant inflammation, mainly by curbing innate and acquired immunity [8]. Increasing interest has been captivated by the broad anti-inflammatory property of IL-37 in autoimmune diseases [11], cancer [12], cardiovascular disease [13] and allergic diseases [14,15]. In this paper, we review recent advance in the roles of IL-37 and several related factors in allergic disorders.

2. Interleukin-37

2.1. The discovery of IL-37

IL-37 was initially reported by three different laboratories [16–18]. It was originally called FIL1ξ [19], IL-1H4 [17], IL-1RP1 [16], IL-1H [18] and IL-1F7 [20], until Charles et al. renamed it IL-37 in 2010 [10]. The human IL-37 gene produces five splice variants including IL-37a-e (Table1), and IL-37b is a most common and best characterized transcript. The human IL-37 gene contains six exons. Exons 4–6 encode the β-clover secondary structure and mainly contribute to biological activity. IL-37a and IL-37d share the same exons 4, 5, and 6 with IL-37b,

Table 2
The role of IL-37 in human disorders (allergic diseases are described in detail in the article).

Disorder	Expression level	Source	Action of IL-37	References
rheumatoid arthritis	increased	peripheral blood CD4(+) T cells and total lymphocytes in RA patients	inhibit TNF-α and IL-6 expression	[27]
systemic lupus erythematosus	increased	plasma	inhibit TNF-α, IL-1β and L-6 expression	[90,91,92]
		peripheral blood mononuclear cells (PBMCs) and serum in SLE patients		[93]
endometriosis	increased	serum	inhibit NF-κB activation	[94]
systemic juvenile idiopathic arthritis	increased	plasma and PBMCs	inhibit IL-6, TNF-αand IL-17 expression	[95]
Hashimoto's thyroiditis	increased	serum	inhibit TNF-α/β, IL-1α/β expression	[96]
adult-onset Still's disease	increased	serum	inhibit IL-6, IL-1β, TNF-α, and IL-18 expression	[97]
primary Sjogren's syndrome	increased	serum	positively correlate with the antibody, IL-18 and IL-18BP expression	[98]
gout	increased	PBMCs	limit monosodium urate crystal-induced innate immune responses	[99]
Guillain-Barre Syndrome	increased	plasma and cerebrospinal fluid	unclear	[100]
influenza A virus	increased	serum	inhibit the replication of IAV RNA	[101]
inflammatory bowel disease	increased	inflamed mucosa	inhibit TNF-α-induced interferon-gamma-inducible protein (IP)-10 expression	[102]
acute anterior uveitis	increased	PBMCs	inhibit IL-1β, IL-6, IL-10, IL-21, IL-23, TNF-α and IFN-γ expression	[103]
proliferative diabetic retinopathy	increased	vitreous fluids	stimulate proangiogenic responses in retinal endothelial cells	[104]
Graves' disease	increased	PBMCs	inhibit IL-6, IL-17 and TNF-α expression	[105]
chronic primary angle closure glaucoma	increased	aqueous humor	unclear	[106]
atherosclerosis	increased	human atherosclerotic plaques	protect against atherosclerosis and strengthen plaque stability	[89]
tuberculosis	increased	serum	induce macrophages towards an M2-like phenotype	[107]
HIV-Infected	increased	PBMCs	may be correlated to the size of the total viral HIV-1 reservoir	[108]
ankylosing spondylitis	increased	PBMCs and serum	inhibit TNF-α, IL-6, IL-17, IL-23 expression	[109]
multiple sclerosis	increased	serum	correlate with disease severity	[110]
autistic spectrum	increased	serum	unclear	[111]
sickle cell anemia	increased	serum	inhibit IL-8 expression	[112]
sepsis	increased	serum	positively correlate with IL-1β, IL-10, neutrophile granulocyte and procalcitonin	[113]
psoriasis	increased	serum	positively correlate with disease severity	[114]
obesity-induced inflammation and insulin resistance	increased	adipose tissue	protect against obesity-induced inflammation and insulin resistance	[55]
Behcet's disease	decreased	PBMCs	1. inhibit the production of ROS by DCs 2. inhibit the activation of ERK1/2, JNK and P38 MAPK in DCs 3. inhibit TH17 and TH1 cell responses 4. inhibit IL-1β, IL-6 and TNF-α expression	[115,116]
	no significant change	serum		[117]
gestational diabetes mellitus	decreased	placenta mononuclear macrophages	negatively correlate with miR-657	[47]
adenomyosis	decreased	ectopic endometria	unclear	[118]
alcoholic steatohepatitis	decreased	liver	inhibit IL-1α/β, TNF-α/β expression	[88]
Vogt-Koyanagi-Harada disease	decreased	PBMCs	inhibit IL-1β, IL-6, and TNF-α induce IL-27 expression.	[119]

so both IL-37a and IL-37d may have biological activity. Exons 1 and 2 of IL-37b can encode a prodomain, which contains a caspase-1 cleavage site that accounts for the transformation from the IL-37b precursor form into mature IL-37b [21]. IL-37a does not contain exons 1 and 2 but includes exon 3, whereas other isoforms do not include, so IL-37a has a unique N-terminus. IL-37c and IL-37e are likely to be inactive since they lack the β-clover secondary structure [17]. IL-37b includes five of the six exons of the IL-37 gene, which leads to biological functions and attracts much interest.

The human IL-37 gene is located on human chromosome 2q12-13 in close proximity to the regulatory regions for the IL-1α and IL-1β genes [22]. IL-1α, IL-1β and IL-37 are transcribed simultaneously in response to lipopolysaccharide (LPS) stimulation in human monocytes and macrophages [22]. The particularity of this position may be related to the immunomodulatory effect of IL-37. Unlike other IL-1 family members, the IL-37 gene is not detected in mice or chimpanzees [23]. Therefore, the numerous studies of IL-37 are based on IL-37 transgenic mice (IL-37tg mice) and recombinant IL-37 (rIL-37) protein treatment in a murine model [10].

2.2. Intracellular function of IL-37

IL-37 can be detected in many human tissues and cells, such as the lymph nodes, bone marrow, lungs, and uterus as well as peripheral blood mononuclear cells (PBMCs), dendritic cells (DCs), monocytes, and tonsil plasma cells [24]. IL-37 is not constitutively expressed in healthy human tissues and cells. Exon 5 contains an instability sequence that regulates the degradation of IL-37 mRNA when the host is in a normal state. Subsequently, IL-37 mRNA and protein levels will rise sharply upon LPS stimulation [25]. Moreover, when the host is exposed to inflammatory stimuli, such as toll-like receptor (TLR) agonists, interferon-γ (IFN-γ), or tumor necrosis factor (TNF-α), IL-37 expression will be readily induced to prevent improper immune responses [10,26]. Investigations have shown that the IL-37 level is elevated or reduced in many diseases, including rheumatoid arthritis (RA) [27], systemic lupus erythematosus (SLE) [28] and inflammatory bowel disease (IBD) [29] (Table2).

As mentioned, the production of IL-37 requires stimulation with LPS. IL-37 nuclear translocation is observed after LPS stimulation for at least 15 h [30]. Subsequently, IL-37 diminishes the expression of TNF-α, IL-1α, and IL-6 as well as that of the chemokine MIP-2 [31]. Consistently, Bulau et al. found that IL-37 also fails to enter the nucleus and diminish the cytokine or chemokine expression when its cleavage site is mutated [32,33]. In this regard, it is reasonable to speculate that caspase-1 and the cleavage site are particularly critical for the nuclear translocation of IL-37. Additionally, the results indicated the nuclear function of IL-37 in the inhibitory effect on innate immune responses [33].

Smad3 is a known mediator of the transforming growth factor beta (TGF-β) pathway. As early as 2004, Grimsby et al. discovered that IL-37 was an interacting protein of Smad3 [34]. Nold et al. found that IL-37b exerts its anti-inflammatory effect through Smad3-dependent mechanisms *in vivo* and *in vitro* [10]. In addition to IL-37b, IL-37d has been found to be involved in similar phenomena. For example, Mingsheng et al. demonstrated that IL-37d can bind to Smad3 and interact with p-Smad3, which contributes to nuclear translocation. Specifically, SIS3, a Smad3-specific inhibitor, can abrogate the anti-inflammatory effect of IL-37d. Consistently, interfering with the production of Smad3 with siRNA can also block the anti-inflammatory function of IL-37d [35]. Hence, we can highlight that the intracellularly inhibitory role of IL-37 relies on Smad3. As Smad3 is also crucial for TGF-β to exert its immuoregulatory and anti-inflammatory effect on immune cells [36–38], it is unclear what is relationship between IL-37 and TGF-β.

2.3. Extracellular function of IL-37

As previously shown, IL-37 can play an anti-inflammatory role in an intracellular manner. When cells are stimulated by inflammatory stimuli, they can produce IL-37. After being processed by caspase-1, IL-37 forms the IL-37-Smad3 complex with Smad3 and then enters the nucleus, acting as a transcription factor that influences the transcription of proinflammatory genes. However, extracellular IL-37 exerts an anti-inflammatory effect by binding to interleukin-18 receptor α (IL-18Rα) and interleukin-1 receptor 8 (IL-1R8).

IL-18, a known proinflammatory cytokine, can bind to IL-18Rα and IL-18Rβ, and then the complex they formed can induce the production of IFN-γ and activate macrophages and other immune cells. IL-37 and IL-18 are structurally similar, both have 2 conserved amino acids [39]. Therefore, IL-37 is likely to be the same as IL-18, which can be combined with IL-18R to volatilize the function of IL-18. A series of experiments proved that IL-37 can bind to IL-18Rα [21,39]. Interestingly, IL-37 has neither an agonistic nor an antagonistic effect on IL-18 [39]. IL-18 has at least a 50-fold higher affinity for IL-18Rα than does IL-37, so IL-37 binds to IL-18Rα in a noncompetitive manner [21]. Following the interaction with IL-18Rα, the complex recruits IL-1R8, previously known as an orphan receptor, rather than IL-18Rβ. Nold-Petry et al. observed the complex IL-37-IL-1R8-IL-18Rα on the surface of human PBMCs [40].

IL-1R8 (TIR8/SIGIRR), a vital member of the IL-1 receptor family, plays salient roles in T cell polarization and TLR-IL-1R-mediated signaling [41]. The accumulated evidence indicates that IL-1R8 is required for the immunomodulatory characteristic of IL-37. Knockdown experiments indicated that silencing IL-1R8 damages the anti-inflammatory effect of IL-37. After the application of an IL-1R8-specific siRNA, IL-1β and TNF levels decreased by 34% (compared to 80% before application) and 49% (compared to 83% before application), respectively [40]. Consequently, *in vivo* experiments showed that IL-37-mediated reductions in IL-6 expression were 64% lower in IL-1R8-deficient IL-37tg mice than in IL-37tg mice [40]. Cavalli et al. observed the protective effect of IL-37 on systemic inflammation when mice received human rIL-37. IL-1R8 deficiency dampened the protective effect of IL-37 [42]. In the synovium from RA patients, the level of IL-1R8 is increased significantly, but there is no a significant difference in the level of IL-37 between RA patients and controls [43]. Similarly, activated CD4 + T cells isolated from patients with AR express higher levels of IL-18R than those from healthy controls [44].

IL-18Binding Protein (IL-18BP), an antagonist of IL-18, has a high affinity for IL-18 (400 pM). Thus, IL-18BP prevents IL-18-induced proinflammatory effects caused by IL-18 binding to other receptors [45]. Additionally, IL-18BP binds to IL-37 to affect anti-inflammatory function. Hence, it is possible that with an increased IL-18BP level, the free IL-37 level will decrease, which would contribute to a less effective anti-inflammatory function for IL-37. Consistently, a low concentration of IL-18BP (0.5 mg/kg) can notably reduce the clinical disease score of collagen-induced arthritis. When the concentration of IL-18BP (1 and 3 mg/kg) is gradually increased, its protective effect gradually became less effective [46].

In general, we conclude that IL-37 plays an immunomodulatory role intracellularly and extracellularly (Fig. 1).

2.4. Signaling pathways

The production, process and biological function of IL-37 are closely related to various signaling pathways. MicroRNA is likely to selectively regulate IL-37 in gestational diabetes mellitus [47]. Experiments with triptonide indicated the possible involvement of the ERK1/2 and p38 MAPK pathways in IL-37 production [48]. Interestingly, in M1 macrophages, the administration of exogenous rIL-37 can suppress p38, ERK, and JNK phosphorylation [49]. In addition, IL-37 induces autophagy by curbing PI3K/AKT/mTOR signaling in various hepatocellular

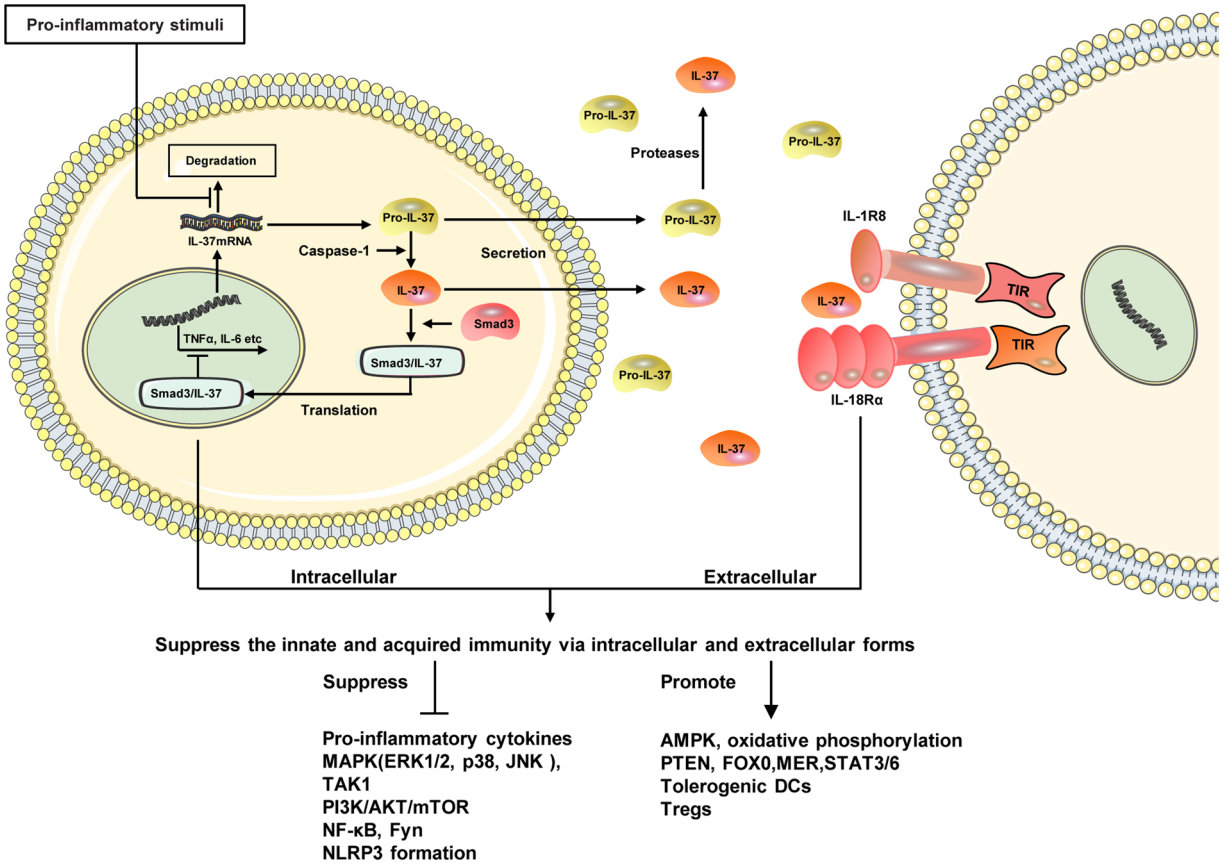


Fig. 1. Diagram depicting the mechanisms of action of IL-37. Proinflammatory stimuli, such as LPS, increase the production of the precursor form of IL-37. The precursor is processed into mature IL-37 by caspase-1. Mature IL-37 interacts with Smad3, which contributes to nuclear translocation and gene transcription regulation. Both the precursor and mature forms of IL-37 are released from cells *via* nonclassical secretory pathways. IL-37 then binds to IL-18Rα and recruits IL-1R8. The complex exerts the extracellular function of IL-37.

carcinoma cells [50]. Nold-Petry et al. demonstrated the critical role of IL-37 not only in the inhibition of the MAPK, NF-κB, TAK1 and Fyn pathways but also in the pseudostarvational effects on the mTOR pathway that activates STAT3, Mer and PTEN and induces p62 (dok) [40].

3. Endogenous IL-37

Although the role of IL-37 in human diseases is less clear, one of the definite features of IL-37 is its anti-inflammatory property. Specifically, IL-37 is a natural suppressor of innate immunity, acquired immunity and inflammation. As early as 2008, Sharma et al. found that the TNF-α, IL-1α, IL-6 and MIP-2 expression in human IL-37b-transfected RAW macrophages was significantly lower than that in empty plasmid-transfected RAW macrophages [31]. Typically, the levels of TNF-α, IL-1α, IL-1β, IL-6, GM-CSF, IL-23, and soluble ICAM-1 are drastically suppressed in RAW-IL-37 cells [10]. Consistently, when researchers silenced or knocked down IL-37 expression, the levels of related proinflammatory cytokines, such as TNF-α, IL-1α, IL-1β, and IL-6, were strongly boosted [10,40]. Adding exogenous antibodies specific for IL-37 to LPS-stimulated monocytes can also increase the expression of TNF-α, IL-6, and IL-1β. Additionally, after stimulation with LPS, the expression levels of various proinflammatory factors (IL-1α, IL-1β, IL-6 and TNF-α) in bone marrow-derived macrophages (BMDMs) isolated from IL-37d-tg mice are lower than those in BMDMs isolated from wild-type mice [35]. As expected, IL-37d-tg mice show less LPS-induced expression of IL-6, TNF, IL-1β, IFN-γ, IL-17A and MCP-1 [35].

4. rIL-37

Using rIL-37 to study the function of IL-37 is also a common and vital method for researchers. Due to the biological characteristics of the IL-37 subgroup, the IL-37b isoform is the most common and effective type of IL-37. As an illustration, adding rIL-37b to LPS-stimulated human blood M1 macrophages reduces the expression of IL-1β, IL-6, and TNF-α [49]. In THP-1 macrophages, after stimulation with LPS, there are increased levels of NF-κB phosphorylation and nuclear translocation, and rIL-37 treatment reduces this intracellular phenomenon [47]. Moreover, rIL-37 treatment can inhibit the expression of CCL11 and the STAT6 signaling pathway. In the house dust mite (HDM)-induced mouse asthma model, airway hyperreactivity (AHR) can be alleviated during the challenge phase [51]. Furthermore, in recent research, rIL-37 could diminish sulfated proteoglycan release and the expression of MMP in human osteoarthritis cartilage explants [52]. Interestingly, a study showed that rIL-37b forms a dimer at high concentrations, which may affect its biological activity [8]. Elan et al. showed that the monomeric form of IL-37 has better inhibitory effects on innate immunity compared to the dimeric form [53]. Accordingly, it is reasonable to speculate that the appropriate application of exogenous human rIL-37 to treat or alleviate inflammatory diseases is a clinical possibility.

In addition to its anti-inflammatory biological function, IL-37 may also be highly relevant to autophagy. After the application of rIL-37 in SMMC-7721 and Huh-7 cells, Zhao et al. found increased numbers of autophagosomes, which indicates that IL-37 may be implicated in autophagy. Moreover, IL-37 may also contribute to apoptosis. Further mechanistic experiments have shown that this effect may be achieved

by curbing the PI3K/AKT/mTOR pathway [50]. On the other hand, IL-37tg mice lose lean body mass by reducing food intake and energy expenditure [54]. An increasing number of studies have shown that IL-37 is critically involved in energy metabolism, obesity and diabetes mellitus [55,56]. From these studies, we could conclude that in addition to its extensive anti-inflammatory effect, IL-37 also plays vital roles in development, such as by affecting metabolism, autophagy and apoptosis, and we will continue to study these roles in depth in the future.

5. The role of IL-37 in asthma

Asthma is a frequent, long-term, inflammatory allergic airway disease with reversible airway obstruction and bronchospasms implicated in excessive T helper 2 (TH2) inflammation and infiltration of inflammatory cells into the airways of the lungs [57]. People with asthma often have symptoms of wheezing, coughing, chest tightness and shortness of breath. Since asthma is a major public health issue in our daily lives, asthma has been attracting much interest. Ovalbumin (OVA) or HDM antigen-induced murine asthma models that mimic human asthma with AHR are extensively studied. According to the increasing research on asthma, we believe that the interleukin family and its pathway as well as TH2 cells play essential roles in the occurrence, development and deterioration of asthma [58].

Compared with that in healthy people, the level of IL-37 in asthmatic patients is decreased significantly [59–61]. More specifically, a study found that the IL-37 protein level in PBMCs isolated from healthy control children is higher than that in PBMCs from children with asthma [60], which was consistent with previous research results [59]. In another study, researchers observed lower levels of IL-37 mRNA in induced sputum cells from asthmatic patients than in those from healthy people, and there were no notable differences between mild asthma and moderate asthma, although higher IL-37 mRNA expression was observed in mild asthma [61]. After combining the anti-inflammatory characteristics of IL-37 and the hallmarks of asthma, it can be speculated that the reduction in IL-37 levels is due to the inability to inhibit the progression of asthma and the imbalance between proinflammatory and anti-inflammatory responses [62]. Hence, the research focus has always been on the roles of IL-37 in the initiation, development and maintenance of asthma.

After applying rIL-37 in mice, the number of eosinophils decreased significantly in the bronchoalveolar lavage fluid (BALF), but the numbers of macrophages, lymphocytes and neutrophils did not change significantly [51,60,63]. However, in contrast with these studies, Huang et al. found that the numbers of macrophages, lymphocytes, neutrophils and eosinophils were significantly reduced in the BALF after rIL-37 administration [64]. This difference may be due to factors such as different experimental models, different experimental methods or test errors. Although there are minor differences, these studies all demonstrated that the administration of rIL-37 can reduce peribronchial and perivascular inflammation and AHR [51,63,64]. Eosinophil infiltration and collagen deposition are important pathophysiological changes in asthma that are prominently diminished after rIL-37 administration [51,63]. Interestingly, the opposite conclusion has also emerged from the study of mucus secretion. Meng et al. found that Muc5ac, a representative mucin in mucus cell hyperplasia, exhibited decreased expression in rIL-37-treated mice [63], while Lv et al. reported that rIL-37 had no effect on Muc5ac [51]. In addition, Zhu et al. documented a remission in mucus secretion and thickened airway walls in rIL-37-treated mice [15].

As we mentioned earlier, IL-18Rα and IL-1R8 are two indispensable components through which IL-37 exerts its anti-inflammatory properties. Lunding et al. demonstrated that the absence of either IL-18Rα or IL-1R8 negated the suppression of airflow inflammation and goblet cell hyperplasia after rIL-37 treatment in mice suffering from asthma [60]. Although there may be a minor discrepancy among the different studies, we can still conclude that IL-37 has a crucial anti-inflammatory role in asthma.

In recent years, one has recognized the importance of TH2 cells, innate immune cells (ILC) and eosinophils in allergic inflammatory responses [58,65]. Lunding et al. found that rIL-37 administration can reduce IL-4, IL-5, IL-6, IL-12, and IL-13 levels in the BALF of asthmatic mice, whereas IL-10 production was unaltered by rIL-37 treatment [60]. Specifically, IL-4, IL-5 and IL-13 are known as TH2-type cytokines, while IL-6 and IL-12 are associated with ILC. Meng and Zhu et al. documented results similar to those of Lunding. Consistently, Charrad et al. identified that the levels of the proinflammatory cytokines TNF-α, IL-β, IL-6 and IL-17A in sputum cells isolated from asthmatic patients are remarkably boosted upon LPS stimulation and reduced after rIL-37 treatment [61]. In addition, Meng and Zhu further demonstrated that CCL5, CCL11, CCL17, CCL22, and IL-17 are highly expressed in experimental mouse lungs and BALF and can be suppressed by rIL-37. Additionally, Meng et al. documented that the local administration of rIL-37 does not affect TH2 systemic sensitization, which indicates a local anti-inflammatory feature of rIL-37 [63]. Contrary to previous research results, the results published by Lv et al. showed that rIL-37 treatment does not affect TH2-associated cytokine production and T cell infiltration in the lungs [51]. This difference may be due to the difference in the doses of rIL-37 used in the two studies and the preparation method of the mouse asthma models.

As we mentioned before, levels of eosinophils, IL-4, IL-13 and CCL11 are boosted and play important roles in IL-37 functions and asthma. Of note, CCL11 is also known as an eosinophil chemotactic protein and selectively recruits eosinophils. Research has identified that IL-4 and IL-13 contribute to the secretion of CCL11 *via* a STAT6-dependent pathway [66–68]. Consistent with decreased eosinophil levels, markedly reduced CCL11 expression is observed in the lungs of asthmatic mice treated with rIL-37. The administration of CCL11 to rIL-37-treated asthmatic mice can strongly restore AHR and eosinophil infiltration. Lv et al. revealed that rIL-37 treatment displays an anti-inflammatory effect by decreasing CCL11 expression [51]. Moreover, CCL11 in asthmatic mice is mainly produced by airway smooth muscle cells (ASMC) and fibroblasts rather than tracheobronchial epithelial cells (TEC) and alveolar epithelial cells (AEC). Interestingly, rIL-37 administration was unable to suppress CCL11 secretion by ASMC and fibroblasts. Researchers subsequently discovered that high expression of IL-18Ra and IL-1R8 is detected in TEC cells, whereas lung fibroblasts, ASMC and AEC express low levels. Further studies demonstrated that rIL-37 reduces the CCL11 expression of ASMC and lung fibroblasts by acting on TEC, and this suppressive effect relies on direct cell contact [51].

In addition to CCL11, thymic stromal lymphopoietin (TSLP) plays a vital role in asthma. Berraies et al. found that high TSLP expression in induced sputum from asthmatic patients can be suppressed by rIL-37 [69]. Meng et al. demonstrated that TSLP is mainly expressed by E-cadherin-positive bronchial epithelium. In particular, TSLP coadministration with IL-37 strongly restored AHR and pathological changes, including eosinophil infiltration, boosted mucus secretion and collagen deposition. Consistently, TSLP coadministration also restored the expression of TH2-type cytokines as well as chemokines. Mechanistically, Meng et al. demonstrated that rIL-37 ameliorates HDM-induced asthma in mice by acting on TSLP via the NF-κB and ERK1/2 pathways [63]. Additionally, Huang et al. identified that IL-37 exerts its protective effect via STAT3 pathways [64]. These signaling pathways associated with IL-37 in asthma are consistent with those identified in previous studies. Collectively, we have all realized that IL-37 plays important roles in the occurrence and development of asthma (Fig. 2).

6. The role of IL-37 in AR

AR is a common chronic inflammatory illness of the nasal mucosa with an incidence rate of 10–40%. AR is more prevalent in children and Westernized countries [70,71]. People with AR typically experience

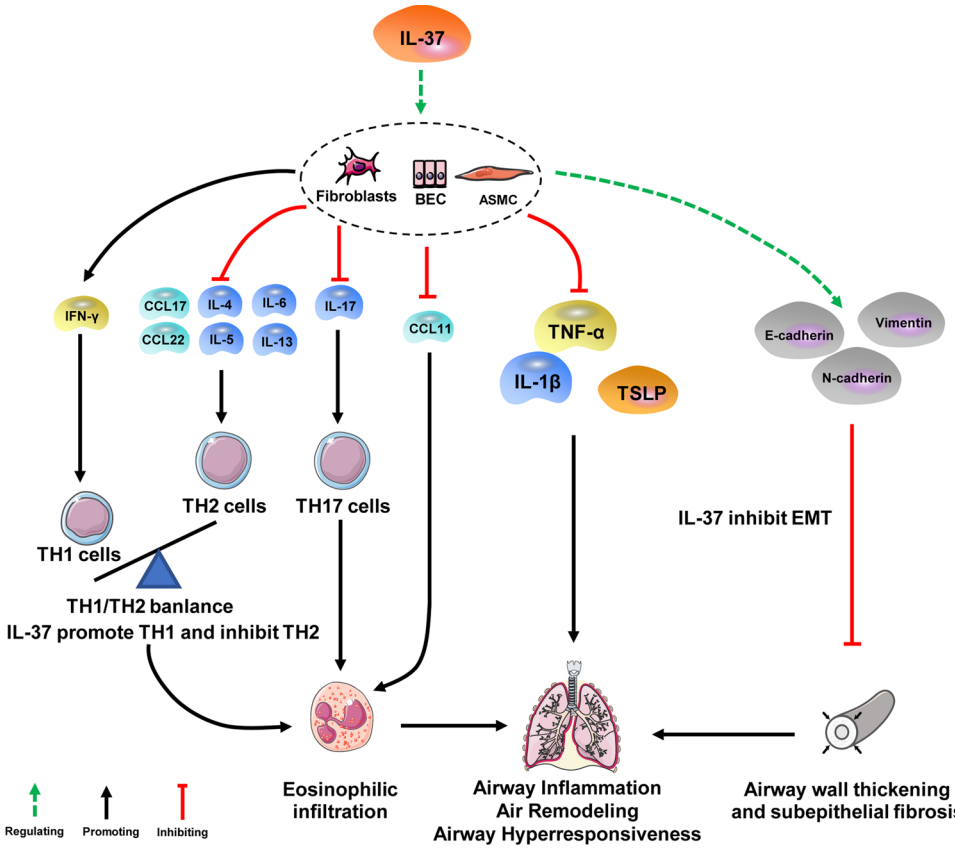


Fig. 2. The role of IL-37 in asthma. IL-37 can act on fibroblasts, bronchial epithelial cells (BEC) and airway smooth muscle cells (ASMC) and affect the expression of related cytokines and chemokines, such as TH2-related cytokines (IL-4, IL-5, etc.), a crucial allergy-related factor (TSLP), and an eosinophil chemotactic protein (CCL11). IL-37 promotes TH1 responses and inhibits TH2 and TH17 responses, which contribute to eosinophilic infiltration. On the other hand, IL-37 can inhibit epithelial-mesenchymal transition (EMT), which is involved in airway wall thickening and subepithelial fibrosis. IL-37 alleviates airway inflammation, remodeling and hyperresponsiveness in the above-mentioned ways.

runny or blocked noses, sneezing, redness, itching and watery eyes. Inherited genetics and specific environmental antigens, such as house dust and pollen, contribute to the initiation of AR [72]. Furthermore, AR is also often closely associated with the initiation, development and deterioration of AA. Emerging evidence indicates that TH1, TH2, and TH17 cells as well as related cytokines play essential roles in the pathological process of AR [73–75].

Studies have found that IL-37 expression is reduced in AR patients [76,77]. Specifically, Liu et al. identified that both the mRNA and protein levels of IL-37 are downregulated in the serum and nasal lavage of patients with AR. Shen et al. found similar downregulation in PBMCs. In addition, Liu et al. also identified that the production of the TH2-type cytokines IL-4, IL-5 and IL-13 is upregulated in the serum and nasal lavage of AR patients and negatively correlates with the serum IL-37 level. Furthermore, these cytokines could be suppressed by rIL-37 [76]. Additionally, Wang et al. validated the inhibitory effect of rIL-37 on IL-4, IL-5 and IL-13 in a mouse model [14]. Consistently, serum Eosinophil Cationic Protein (ECP) and specific IgE levels are boosted and can be inhibited by rIL-37, and these effects have also been verified in AR mice [14,76]. Similar to TH2 cytokines, IL-17 has significantly augmented expression in both AR patients and murine models compared with the appropriate control, and rIL-37 inhibits the proliferation and differentiation of TH17 cells [14,44,77,78]. There are data indicating that ROR-γt, a transcription factor that can induce IL-17 expression, is highly expressed in the nasal mucosa of AR mice and that the expression of IL-27, a key cytokine suppressor of IL-17, is dampened in AR patients but can be restored by rIL-37 treatment [77–80]. Apart from the focus on TH2 and TH17 cells, TH1 and regulatory T (Treg) cells also attract much attention [81]. Contrary to the inhibitory effect of IL-37 on TH2 and TH17 cells, IL-37 exhibits a limited and minimal effect on TH1 and Treg cells [14,76,78]. Consistently, studies have shown that after rIL-37 administration, the expression levels of T-bet, IL-10 and Foxp3 do not change significantly, suggesting that IL-37 is ineffective against TH1 and Treg cells [14,44,76,78]. The expression of IL-10 in AR remains to be explored. While some researchers have documented decreased IL-10 production in AR, others have reported that the IL-10 level remains unchanged [14,76–78].

Referring to the therapeutic effect of rIL-37, sneezing and nasal rubbing symptoms in an HDM/OVA-induced AR murine model are relieved after rIL-37 administration [14,78]. When applying Mometasone Furoate to children with AR, Liu et al. detected elevated production of IL-37 in the nasal lavage and a negative correlation between the level of IL-37 and symptom scores [76]. Mechanistically, a study by Liu et al. noted that IL-37 attenuates TH2-type immune responses in AR via the MAPK and PI3K signaling pathways [76]. Wang et al. identified that IL-37 inhibits TH2- and TH17-related factors by suppressing the activation of STAT3/STAT6 signaling [14]. All of these results demonstrate the important role of IL-37 in AR (Fig. 3).

7. The role of IL-37 in AD

AD comprises both allergic contact dermatitis (ACD) and atopic dermatitis types. AD morbidity is dramatically rising in the world and has become a major public health threat [82]. Innate and acquired immunity play important roles in ACD. TH cells and related cytokines are closely related to the initiation and development of ACD [83]. Atopic dermatitis is a kind of inflammation of the skin characterized by skin irritation, itching, rash and cracked skin. Atopic dermatitis often starts in childhood, resulting from immune abnormalities, impaired skin barriers and allergen permeation. TH2 immune responses play an essential role in the pathogenesis of atopic dermatitis [84].

Contact hypersensitivity (CHS) is a vital characteristic of AD. Luo et al. documented that compared with wild-type mice, IL-37tg mice show fewer allergic symptoms, such as ear swelling, after hapten application. Luo et al. further found that high IL-37 expression in DCs during sensitization may contribute to helping hosts reduce CHS severity. Subsequently, researchers realized that the expression of IL-37 in DCs influences DC maturation, which is responsible for the suppressed

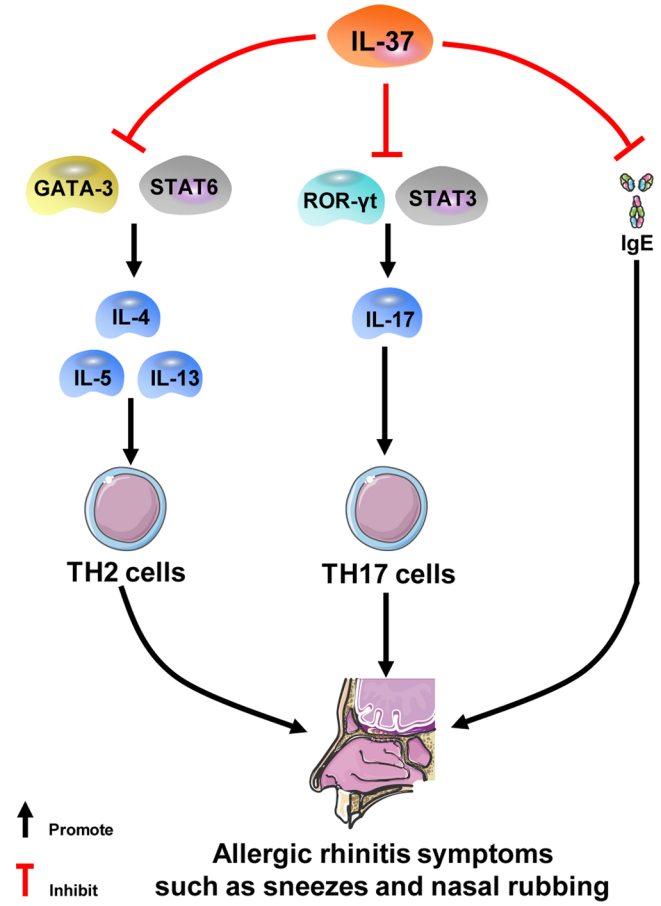


Fig. 3. The role of IL-37 in allergic rhinitis. IL-37 can inhibit transcription factors that are essential for the differentiation of the TH2 and TH17 cells, including GATA-3, ROR-γt, STAT3 and STAT6. IL-37 also suppresses the levels of IgE, which is an important antibody isotype in responses to allergens. IL-37 alleviates allergic symptoms, such as sneezing and nasal rubbing, by inhibiting TH2 and TH17 cells and IgE.

CHS. Furthermore, IL-37 damaged the ability of DCs to activate innate and acquired immunity and induced Treg cell development during the sensitization stage [85].

On the other hand, Fujita et al. found that the serum IL-37 level is notably boosted in atopic dermatitis patients. Consistent with the serum level, the skin IL-37 level was also elevated. Interestingly, IL-37 protein could not be detected in keratinocytes, dermal fibroblasts or PBMCs, but IL-37 mRNA could be identified in these cells [86]. In addition, Da Rosa et al. found that atopic dermatitis skin displays higher production of IL-37 than non-atopic dermatitis skin. Additionally, IL-10 and FoxP3 level were highly boosted in atopic dermatitis skin[95]. Ghosh et al. identified that IL-37 is the top augmented gene in nonlesional atopic dermatitis by multiple transcriptome data analysis. However, the researchers interestingly found higher expression of the IL-4 and IL-13 receptor genes in the database, whereas IL-4 and IL-13 gene expression did not change significantly [87].

All of the above studies have shown that IL-37 is closely related to AD. IL-37 is likely to be involved in AD by regulating TH2 cytokines, chemokines, and DC maturation and function. However, in general, compared to that in other diseases, the research on the role and function of IL-37 in AD is not abundant, and in the future, we need to focus more on AD, which is decidedly worth exploring.

8. Discussion

The noticeable anti-inflammatory and immunoregulatory characteristics identified from numerous studies reveal that the novel cytokine of the IL-1 family is able to curb rampant inflammation and protect hosts from various inflammatory disorders. IL-37 inhibits the maturation of some related inflammatory cells, the expression of cytokines and the activation of a series of signaling pathways through both intracellular and extracellular processes. Extracellularly, IL-37 exerts an inhibitory effect through binding to IL-18Rα and then recruiting IL-1R8. Intracellularly, after processing by caspase-1, IL-37 forms the IL-37-Smad3 complex with Smad3 and then enters the nucleus, acting as a transcription factor to influence transcription, cell maturation and cytokine production.

In recent years, our understanding of the role and function of IL-37 in various diseases, such as autoimmune diseases, cancer, and atherosclerosis, has greatly increased. Notably, considerable data has gradually highlighted the ability of IL-37 to protect against allergic diseases. However, our current knowledge of IL-37 in allergic diseases is far from complete, and the specific role and mechanism of IL-37 in allergic diseases are still unclear. For instance, studies on IL-37 and AD are still insufficient. Far more research could focus on the exact effects of IL-37 on TH1, TH2, TH17 and Treg cells in AD and dissect the signaling pathways that are involved in the function of IL-37 during pathological changes. Defining the exact functions and pathways through which IL-37 impacts allergic inflammatory processes may be beneficial to finding credible ways to strongly ameliorate allergic disorders. As we mentioned, IL-37tg mice exhibit fewer clinical symptoms and pathological changes when used to model allergic diseases than control mice. Additionally, rIL-37 treatment exerts a considerable protective effect on murine models of allergic disease. Likewise, rIL-37-treated mice and IL-37tg mice display similar conditions in various disorders, including alcoholic liver disease [88], colitis [26], atherosclerosis [89], asthma [15]. These previous studies raise the possibility of using IL-37 as a novel therapeutic target in allergic diseases. Overall, we emphasized the significant potential for clinical treatment and the role and function of IL-37 in asthma, AR and AD. In the future, additional careful investigations are urgently needed to demonstrate the promising therapeutic potential of IL-37.

Author contributions

Conception and design: W.S. and S.G.Z; Drafting and revising of the article: W.S., Z.H., L.X., H.L. and X.L.J.A.B; Final approval: W.S. and S.G.Z.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by the National Key R&D Program of China (2017YFA0105800), the Natural Science Foundation of China (81670897, 81600731 and U1601226), Guangdong Natural Science Funds for Distinguished Young Scholar (2016A030306006);

References

[1] D.R. Wesemann, C.R. Nagler, T. Microbiome, Timing, and barrier function in the context of allergic disease, Immunity 44 (4) (2016) 728–738.
[2] M. Asaria, S. Dhami, R. van Ree, R. Gerth van Wijk, A. Muraro, G. Roberts, A. Sheikh, Health economic analysis of allergen immunotherapy for the management of allergic rhinitis, asthma, food allergy and venom allergy: a systematic overview, Allergy 73 (2) (2018) 269–283.
[3] O.J. Lawless, J.A. Bellanti, M.L. Brown, K. Sandberg, J.G. Umans, L. Zhou, W. Chen, J. Wang, K. Wang, S.G. Zheng, In vitro induction of T regulatory cells by a methylated CpG DNA sequence in humans: potential therapeutic applications in allergic and autoimmune diseases, Allergy Asthma Proc. 39 (2) (2018) 143–152.
[4] C.G. Mortz, J.M. Lauritsen, C. Bindslev-Jensen, K.E. Andersen, Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in

adolescents. The odense adolescence cohort study on atopic diseases and dermatitis, Br. J. Dermatol. 144 (3) (2001) 523–532.
[5] Q.N. Yu, Y.B. Guo, X. Li, C.L. Li, W.P. Tan, X.L. Fan, Z.L. Qin, D. Chen, W.P. Wen, S.G. Zheng, Q.L. Fu, ILC2 frequency and activity are inhibited by glucocorticoid treatment via STAT pathway in patients with asthma, Allergy 73 (9) (2018) 1860–1870.
[6] A.G. Besnard, D. Togbe, I. Couillin, Z. Tan, S.G. Zheng, F. Erard, M. Le Bert, V. Quesniaux, B. Ryffel, Inflammasome-IL-1-Th17 response in allergic lung inflammation, J. Mol. Cell Biol. 4 (1) (2012) 3–10.
[7] F. Madouri, N. Guillou, L. Fauconnier, T. Marchiol, N. Rouxel, P. Chenuet, A. Ledru, L. Apetoh, F. Ghiringhelli, M. Chamaillard, S.G. Zheng, F. Trovero, V.F. Quesniaux, B. Ryffel, D. Togbe, Caspase-1 activation by NLRP3 inflammasome dampens IL-33-dependent house dust mite-induced allergic lung inflammation, J. Mol. Cell Biol. 7 (4) (2015) 351–365.
[8] G. Cavalli, C.A. Dinarello, Suppression of inflammation and acquired immunity by IL-37, Immunol. Rev. 281 (1) (2018) 179–190.
[9] A. Mantovani, C.A. Dinarello, M. Molgora, C. Garlanda, Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity, Immunity 50 (4) (2019) 778–795.
[10] M.F. Nold, C.A. Nold-Petry, J.A. Zepp, B.E. Palmer, P. Bufler, C.A. Dinarello, IL-37 is a fundamental inhibitor of innate immunity, Nat. Immunol. 11 (11) (2010) 1014–1022.
[11] W.D. Xu, Y. Zhao, Y. Liu, Insights into IL-37, the role in autoimmune diseases, Autoimmun. Rev. 14 (12) (2015) 1170–1175.
[12] A. Abulkhir, S. Samarani, D. Amre, M. Duval, E. Haddad, D. Sinnett, J.M. Leclerc, C. Diorio, A. Ahmad, A protective role of IL-37 in cancer: a new hope for cancer patients, J. Leukoc. Biol. 101 (2) (2017) 395–406.
[13] S. Pfeiler, H. Winkels, M. Kelm, N. Gerdes, IL-1 family cytokines in cardiovascular disease, Cytokine 122 (2017) 154215.
[14] J. Wang, Y. Shen, C. Li, C. Liu, Z.H. Wang, Y.S. Li, X. Ke, G.H. Hu, IL-37 attenuates allergic process via STAT6/STAT3 pathways in murine allergic rhinitis, Int. Immunopharmacol. 69 (2019) 27–33.
[15] J. Zhu, J. Dong, L. Ji, P. Jiang, T.F. Leung, D. Liu, L.G. Ng, M.S. Tsang, D. Jiao, C.W. Lam, C.K. Wong, Anti-Allergic Inflammatory Activity of Interleukin-37 Is Mediated by Novel Signaling Cascades in Human Eosinophils, Front. Immunol. 9 (2018) 1445.
[16] S.J. Busfield, C.A. Comrack, G. Yu, T.W. Chickering, J.S. Smutko, H. Zhou, K.R. Leiby, L.M. Holmgren, D.P. Gearing, Y. Pan, Identification and gene organization of three novel members of the IL-1 family on human chromosome 2, Genomics 66 (2) (2000) 213–216.
[17] S. Kumar, P.C. McDonnell, R. Lehr, L. Tierney, M.N. Tzimas, D.E. Griswold, E.A. Capper, R. Tal-Singer, G.I. Wells, M.L. Doyle, P.R. Young, Identification and initial characterization of four novel members of the interleukin-1 family, J. Biol. Chem. 275 (14) (2000) 10308–10314.
[18] G. Pan, P. Risser, W. Mao, D.T. Baldwin, A.W. Zhong, E. Filvaroff, D. Yansura, L. Lewis, C. Eigenbrot, W.J. Henzel, R. Vandlen, IL-1H, an interleukin 1-related protein that binds IL-18 receptor/IL-1Rrp, Cytokine 13 (1) (2001) 1–7.
[19] D.E. Smith, B.R. Renshaw, R.R. Ketchem, M. Kubin, K.E. Garka, J.E. Sims, Four new members expand the interleukin-1 superfamily, J. Biol. Chem. 275 (2) (2000) 1169–1175.
[20] E. Dunn, J.E. Sims, M.J. Nicklin, L.A. O'Neill, Annotating genes with potential roles in the immune system: six new members of the IL-1 family, Trends Immunol. 22 (10) (2001) 533–536.
[21] S. Kumar, C.R. Hanning, M.R. Brigham-Burke, D.J. Rieman, R. Lehr, S. Khandekar, R.B. Kirkpatrick, G.F. Scott, J.C. Lee, F.J. Lynch, W. Gao, A. Gambotto, M.T. Lotze, Interleukin-1F7B (IL-1H4/IL-1F7) is processed by caspase-1 and mature IL-1F7B binds to the IL-18 receptor but does not induce IFN-gamma production, Cytokine 18 (2) (2002) 61–71.
[22] N. Sharaf, M.J. Nicklin, F.S. di Giovine, Long-range DNA interactions at the IL-1/IL-36/IL-37 gene cluster (2q13) are induced by activation of monocytes, Cytokine 68 (1) (2014) 16–22.
[23] T.L. Newman, E. Tuzun, V.A. Morrison, K.E. Hayden, M. Ventura, S.D. McGrath, M. Rocchi, E.E. Eichler, A genome-wide survey of structural variation between human and chimpanzee, Genome Res. 15 (10) (2005) 1344–1356.
[24] H. Jia, J. Liu, B. Han, Reviews of Interleukin-37: functions, receptors, and roles in diseases, Biomed Res. Int. 2018 (2018) 3058640.
[25] P. Bufler, F. Gamboni-Robertson, T. Azam, S.H. Kim, C.A. Dinarello, Interleukin-1 homologues IL-1F7b and IL-18 contain functional mRNA instability elements within the coding region responsive to lipopolysaccharide, Biochem. J. 381 (Pt 2) (2004) 503–510.
[26] E.N. McNamee, J.C. Masterson, P. Jedlicka, M. McManus, A. Grenz, C.B. Collins, M.F. Nold, C. Nold-Petry, P. Bufler, C.A. Dinarello, J. Rivera-Nieves, Interleukin 37 expression protects mice from colitis, Proc. Natl. Acad. Sci. U. S. A. 108 (40) (2011) 16711–16716.
[27] L. Wang, Y. Wang, L. Xia, H. Shen, J. Lu, Elevated frequency of IL-37- and IL-18Ralpha-positive T cells in the peripheral blood of rheumatoid arthritis patients, Cytokine 110 (2018) 291–297.
[28] J. Godsell, I. Rudloff, R. Kandane-Rathnayake, A. Hoi, M.F. Nold, E.F. Morand, J. Harris, Clinical associations of IL-10 and IL-37 in systemic lupus erythematosus, Sci. Rep. 6 (2016) 34604.
[29] Z. Chen, S. Wang, L. Li, Z. Huang, K. Ma, Anti-inflammatory effect of IL-37-Producing T-cell population in DSS-induced chronic inflammatory bowel disease in mice, Int. J. Mol. Sci. 19 (12) (2018).
[30] R. Ross, J. Grimmel, S. Goedicke, A.M. Mobus, A.M. Bulau, P. Bufler, S. Ali, M.U. Martin, Analysis of nuclear localization of interleukin-1 family cytokines by flow cytometry, J. Immunol. Methods 387 (1–2) (2013) 219–227.
[31] S. Sharma, N. Kulk, M.F. Nold, R. Graf, S.H. Kim, D. Reinhardt, C.A. Dinarello, P. Bufler, The IL-1 family member 7b translocates to the nucleus and down-regulates proinflammatory cytokines, J. Immunol. 180 (8) (2008) 5477–5482.
[32] A.M. Bulau, M.F. Nold, S. Li, C.A. Nold-Petry, M. Fink, A. Mansell, T. Schwerd, J. Hong, A. Rubartelli, C.A. Dinarello, P. Bufler, Role of caspase-1 in nuclear translocation of IL-37, release of the cytokine, and IL-37 inhibition of innate immune responses, Proc. Natl. Acad. Sci. U. S. A. 111 (7) (2014) 2650–2655.
[33] S. Li, J. Amo-Aparicio, C.P. Neff, I.W. Tengesdal, T. Azam, B.E. Palmer, R. Lopez-Vales, P. Bufler, C.A. Dinarello, Role for nuclear interleukin-37 in the suppression of innate immunity, Proc. Natl. Acad. Sci. U. S. A. (2019) [Epub ahead of print].
[34] S. Grimsby, H. Jaensson, A. Dubrovska, M. Lomnytska, U. Hellman, S. Souchelnytskyi, Proteomics-based identification of proteins interacting with Smad3: SREBP-2 forms a complex with Smad3 and inhibits its transcriptional activity, FEBS Lett. 577 (1–2) (2004) 93–100.
[35] M. Zhao, Y. Li, C. Guo, L. Wang, H. Chu, F. Zhu, Y. Li, X. Wang, Q. Wang, W. Zhao, Y. Shi, W. Chen, L. Zhang, IL-37 isoform D downregulates pro-inflammatory cytokines expression in a Smad3-dependent manner, Cell Death Dis. 9 (6) (2018) 582.
[36] L. Lu, J. Wang, F. Zhang, Y. Chai, D. Brand, X. Wang, D.A. Horwitz, W. Shi, S.G. Zheng, Role of SMAD and non-SMAD signals in the development of Th17 and regulatory T cells, J. Immunol. 184 (8) (2010) 4295–4306.
[37] L. Lu, J. Ma, X. Wang, J. Wang, F. Zhang, J. Yu, G. He, B. Xu, D.D. Brand, D.A. Horwitz, W. Shi, S.G. Zheng, Synergistic effect of TGF-beta superfamily members on the induction of Foxp3+ Treg, Eur. J. Immunol. 40 (1) (2010) 142–152.
[38] S.G. Zheng, J.H. Wang, J.D. Gray, H. Soucier, D.A. Horwitz, Natural and induced CD4+CD25+ cells educate CD4+CD25- cells to develop suppressive activity: the role of IL-2, TGF-beta, and IL-10, J. Immunol. 172 (9) (2004) 5213–5221.
[39] P. Bufler, T. Azam, F. Gamboni-Robertson, L.L. Reznikov, S. Kumar, C.A. Dinarello, S.H. Kim, A complex of the IL-1 homologue IL-1F7b and IL-18-binding protein reduces IL-18 activity, Proc. Natl. Acad. Sci. U. S. A. 99 (21) (2002) 13723–13728.
[40] C.A. Nold-Petry, C.Y. Lo, I. Rudloff, K.D. Elgass, S. Li, M.P. Gantier, A.S. Lotz-Havla, S.W. Gersting, S.X. Cho, J.C. Lao, A.M. Ellisdon, B. Rotter, T. Azam, N.E. Mangan, F.J. Rossello, J.C. Whisstock, P. Bufler, C. Garlanda, A. Mantovani, C.A. Dinarello, M.F. Nold, IL-37 requires the receptors IL-18Ralpha and IL-1R8 (SIGIRR) to carry out its multifaceted anti-inflammatory program upon innate signal transduction, Nat. Immunol. 16 (4) (2015) 354–365.
[41] C. Garlanda, H.J. Anders, A. Mantovani, TIR8/SIGIRR: an IL-1R/TLR family member with regulatory functions in inflammation and T cell polarization, Trends Immunol. 30 (9) (2009) 439–446.
[42] G. Cavalli, J.N. Justice, K.E. Boyle, A. D'Alessandro, E.Z. Eisenmesser, J.J. Herrera, K.C. Hansen, T. Nemkov, R. Stienstra, C. Garlanda, A. Mantovani, D.R. Seals, L. Dagna, L.A. Joosten, D.B. Ballak, C.A. Dinarello, Interleukin 37 reverses the metabolic cost of inflammation, increases oxidative respiration, and improves exercise tolerance, Proc. Natl. Acad. Sci. U. S. A. 114 (9) (2017) 2313–2318.
[43] G. Cavalli, M. Koenders, V. Kalabokis, J. Kim, A.C. Tan, C. Garlanda, A. Mantovani, L. Dagna, L.A. Joosten, C.A. Dinarello, Treating experimental arthritis with the innate immune inhibitor interleukin-37 reduces joint and systemic inflammation, Rheumatology (Oxford) 55 (12) (2016) 2220–2229.
[44] C. Li, Y. Shen, J. Wang, Z.X. Ma, X. Ke, Z.H. Wang, S.L. Hong, G.H. Hu, Increased expression of IL-1R8 and a possible immunomodulatory role of its ligand IL-37 in allergic rhinitis patients, Int. Immunopharmacol. 60 (2018) 152–159.
[45] G. Kaplanski, Interleukin-18: Biological properties and role in disease pathogenesis, Immunol. Rev. 281 (1) (2018) 138–153.
[46] N.K. Banda, A. Vondracek, D. Kraus, C.A. Dinarello, S.H. Kim, A. Bendele, G. Senaldi, W.P. Arend, Mechanisms of inhibition of collagen-induced arthritis by murine IL-18 binding protein, J. Immunol. 170 (4) (2003) 2100–2105.
[47] P. Wang, H. Wang, C. Li, X. Zhang, X. Xiu, P. Teng, Z. Wang, Dysregulation of microRNA-657 influences inflammatory response via targeting interleukin-37 in gestational diabetes mellitus, J. Cell. Physiol. 234 (5) (2018) 7141–7148.
[48] L. He, Z. Liang, F. Zhao, L. Peng, Z. Chen, Modulation of IL-37 expression by triptolide and triptonide in THP-1 cells, Cell. Mol. Immunol. 12 (4) (2015) 515–518.
[49] S. Li, C.P. Neff, K. Barber, J. Hong, Y. Luo, T. Azam, B.E. Palmer, M. Fujita, C. Garlanda, A. Mantovani, S. Kim, C.A. Dinarello, Extracellular forms of IL-37 inhibit innate inflammation in vitro and in vivo but require the IL-1 family decoy receptor IL-1R8, Proc. Natl. Acad. Sci. U. S. A. 112 (8) (2015) 2497–2502.
[50] T.T. Li, D. Zhu, T. Mou, Z. Guo, J.L. Pu, Q.S. Chen, X.F. Wei, Z.J. Wu, IL-37 induces autophagy in hepatocellular carcinoma cells by inhibiting the PI3K/AKT/mTOR pathway, Mol. Immunol. 87 (2017) 132–140.
[51] J. Lv, Y. Xiong, W. Li, X. Cui, X. Cheng, Q. Leng, R. He, IL-37 inhibits IL-4/IL-13-induced CCL11 production and lung eosinophilia in murine allergic asthma, Allergy 73 (8) (2018) 1642–1652.
[52] E.W. van Geffen, A.P.M. van Caam, W. Schreurs, F.A. van de Loo, P. van Lent, M.I. Koenders, C.S. Thudium, A.C. Bay-Jensen, E.N. Blaney Davidson, P.M. van der Kraan, IL-37 diminishes proteoglycan loss in human OA cartilage: donor-specific link between IL-37 and MMP-3, Osteoarthr. Cartil. 27 (1) (2018) 148–157.
[53] E.Z. Eisenmesser, A. Gottschlich, J.S. Redzic, N. Paukovich, J.C. Nix, T. Azam, L. Zhang, R. Zhao, J.S. Kieft, E. The, X. Meng, C.A. Dinarello, Interleukin-37 monomer is the active form for reducing innate immunity, Proc. Natl. Acad. Sci. U. S. A. 116 (12) (2019) 5514–5522.
[54] E.N. Kuipers, A.D. van Dam, D.B. Ballak, E.A. de Wit, C.A. Dinarello, R. Stienstra, J.A. van Diepen, P.C.N. Rensen, M.R. Boon, IL-37 expression reduces lean body mass in mice by reducing food intake, Int. J. Mol. Sci. 19 (8) (2018).
[55] D.B. Ballak, J.A. van Diepen, A.R. Moschen, H.J. Jansen, A. Hijmans, G.J. Groenhof, F. Leenders, P. Bufler, M.V. Boekschoten, M. Muller, S. Kersten,

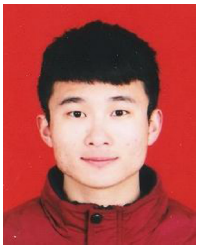
S. Li, S. Kim, H. Eini, E.C. Lewis, L.A. Joosten, H. Tilg, M.G. Netea, C.J. Tack, C.A. Dinarello, R. Stienstra, IL-37 protects against obesity-induced inflammation and insulin resistance, Nat. Commun. 5 (2014) 4711.
[56] D.B. Ballak, S. Li, G. Cavalli, J.L. Stahl, I.W. Tengesdal, J.A. van Diepen, V. Kluck, B. Swartzwelter, T. Azam, C.J. Tack, R. Stienstra, T. Mandrup-Poulsen, D.R. Seals, C.A. Dinarello, Interleukin-37 treatment of mice with metabolic syndrome improves insulin sensitivity and reduces pro-inflammatory cytokine production in adipose tissue, J. Biol. Chem. 293 (37) (2018) 14224–14236.
[57] W. Xu, Q. Lan, M. Chen, H. Chen, N. Zhu, X. Zhou, J. Wang, H. Fan, C.S. Yan, J.L. Kuang, D. Warburton, D. Togbe, B. Ryffel, S.G. Zheng, W. Shi, Adoptive transfer of induced-Treg cells effectively attenuates murine airway allergic inflammation, PLoS One 7 (7) (2012) e40314.
[58] P.J. Barnes, Targeting cytokines to treat asthma and chronic obstructive pulmonary disease, Nat. Rev. Immunol. 18 (7) (2018) 454–466.
[59] D. Raedler, N. Ballenberger, E. Klucker, A. Bock, R. Otto, O. Prazeres da Costa, O. Holst, T. Illig, T. Buch, E. von Mutius, B. Schaub, Identification of novel immune phenotypes for allergic and nonallergic childhood asthma, J. Allergy Clin. Immunol. 135 (1) (2015) 81–91.
[60] L. Lunding, S. Webering, C. Vock, A. Schroder, D. Raedler, B. Schaub, H. Fehrenbach, M. Wegmann, IL-37 requires IL-18Ralpha and SIGIRR/IL-1R8 to diminish allergic airway inflammation in mice, Allergy 70 (4) (2015) 366–373.
[61] R. Charrad, A. Berraies, B. Hamdi, J. Ammar, K. Hamzaoui, A. Hamzaoui, Anti-inflammatory activity of IL-37 in asthmatic children: Correlation with inflammatory cytokines TNF-alpha, IL-beta, IL-6 and IL-17A, Immunobiology 221 (2) (2016) 182–187.
[62] Y. Luo, S.G. Zheng, Hall of fame among pro-inflammatory cytokines: Interleukin-6 gene and its transcriptional regulation mechanisms, Front. Immunol. 7 (2016) 604.
[63] P. Meng, Z.G. Chen, T.T. Zhang, Z.Z. Liang, X.L. Zou, H.L. Yang, H.T. Li, IL-37 alleviates house dust mite-induced chronic allergic asthma by targeting TSLP through the NF-kappaB and ERK1/2 signaling pathways, Immunol. Cell Biol. 97 (4) (2018) 403–415.
[64] N. Huang, K. Liu, J. Liu, X. Gao, Z. Zeng, Y. Zhang, J. Chen, Interleukin-37 alleviates airway inflammation and remodeling in asthma via inhibiting the activation of NF-kappaB and STAT3 signalings, Int. Immunopharmacol. 55 (2018) 198–204.
[65] K.F. Chung, Targeting the interleukin pathway in the treatment of asthma, Lancet 386 (9998) (2015) 1086–1096.
[66] R. He, H.Y. Kim, J. Yoon, M.K. Oyoshi, A. MacGinnitie, S. Goya, E.J. Freyschmidt, P. Bryce, A.N. McKenzie, D.T. Umetsu, H.C. Oettgen, R.S. Geha, Exaggerated IL-17 response to epicutaneous sensitization mediates airway inflammation in the absence of IL-4 and IL-13, J. Allergy Clin. Immunol. 124 (4) (2009) 761–70 e1.
[67] Q. Peng, T. Matsuda, S.J. Hirst, Signaling pathways regulating interleukin-13-stimulated chemokine release from airway smooth muscle, Am. J. Respir. Crit. Care Med. 169 (5) (2004) 596–603.
[68] S.E. Wenzel, J.B. Trudeau, S. Barnes, X. Zhou, M. Cundall, J.Y. Westcott, K. McCord, H.W. Chu, TGF-beta and IL-13 synergistically increase eotaxin-1 production in human airway fibroblasts, J. Immunol. 169 (8) (2002) 4613–4619.
[69] A. Berraies, B. Hamdi, J. Ammar, K. Hamzaoui, A. Hamzaoui, Increased expression of thymic stromal lymphopoietin in induced sputum from asthmatic children, Immunol. Lett. 178 (2016) 85–91.
[70] D.P. Skoner, Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis, J. Allergy Clin. Immunol. 108 (1 Suppl) (2001) S2–8.
[71] A. Togias, Rhinitis and asthma: evidence for respiratory system integration, J. Allergy Clin. Immunol. 111 (6) (2003) 1171-83; quiz 1184.
[72] X. Chen, L. Chang, X. Li, J. Huang, L. Yang, X. Lai, Z. Huang, Z. Wang, X. Wu, J. Zhao, J.A. Bellanti, S.G. Zheng, G. Zhang, Tc17/IL-17A up-regulated the expression of MMP-9 via NF-kappaB pathway in nasal epithelial cells of patients with chronic rhinosinusitis, Front. Immunol. 9 (2018) 2121.
[73] A.N. Greiner, P.W. Hellings, G. Rotiroti, G.K. Scadding, Allergic rhinitis, Lancet 378 (9809) (2011) 2112–2122.
[74] A.O. Eifan, N.T. Orban, M.R. Jacobson, S.R. Durham, Severe persistent allergic rhinitis. Inflammation but no histologic features of structural upper airway remodeling, Am. J. Respir. Crit. Care Med. 192 (12) (2015) 1431–1439.
[75] R.K. Gupta, K. Gupta, P.D. Dwivedi, Pathophysiology of IL-33 and IL-17 in allergic disorders, Cytokine Growth Factor Rev. 38 (2017) 22–36.
[76] W. Liu, L. Deng, Y. Chen, C. Sun, J. Wang, L. Zhou, H. Li, R. Luo, Anti-inflammatory effect of IL-37b in children with allergic rhinitis, Mediators Inflamm. 2014 (2014) 746846.
[77] Y. Shen, X. Ke, L. Yun, G.H. Hu, H.Y. Kang, S.L. Hong, Decreased expression of interleukin-37 and its anti-inflammatory effect in allergic rhinitis, Mol. Med. Rep. 17 (1) (2018) 1333–1339.
[78] D.H. Kim, S.W. Kim, S.W. Kim, J.M. Kang, Interleukin-37 relieves allergic inflammation in a house dust mite allergic rhinitis murine model, Iran. J. Allergy Asthma Immunol. 16 (5) (2017) 404–417.
[79] K. Hirahara, K. Ghoreschi, X.P. Yang, H. Takahashi, A. Laurence, G. Vahedi, G. Sciume, A.O. Hall, C.D. Dupont, L.M. Francisco, Q. Chen, M. Tanaka, Y. Kanno, H.W. Sun, A.H. Sharpe, C.A. Hunter, J.J. O'Shea, Interleukin-27 priming of T cells controls IL-17 production in trans via induction of the ligand PD-L1, Immunity 36 (6) (2012) 1017–1030.
[80] S. Rutz, W. Ouyang, The itch to degrade ROR-gammat, Nat. Immunol. 17 (8) (2016) 898–900.
[81] W. Su, H. Fan, M. Chen, J. Wang, D. Brand, X. He, V. Quesniaux, B. Ryffel, L. Zhu, D. Liang, S.G. Zheng, Induced CD4+ forkhead box protein-positive T cells inhibit mast cell function and established contact hypersensitivity through TGF-beta1, J. Allergy Clin. Immunol. 130 (2) (2012) 444-52 e7.
[82] L.S. Fonacier, S.C. Dreskin, D.Y. Leung, Allergic skin diseases, J. Allergy Clin. Immunol. 125 (2 Suppl 2) (2010) S138–49.
[83] M. Baeck, A. Herman, L. de Montjoye, E. Hendrickx, P. Cheou, P.M. Cochez, L. Dumoutier, Increased expression of interleukin-9 in patients with allergic contact dermatitis caused by p-phenylenediamine, Contact Derm. 79 (6) (2018) 346–355.
[84] D.Y. Leung, Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic diseases, J. Allergy Clin. Immunol. 96 (3) (1995) 302-18; quiz 319.
[85] Y. Luo, X. Cai, S. Liu, S. Wang, C.A. Nold-Petry, M.F. Nold, P. Bufler, D. Norris, C.A. Dinarello, M. Fujita, Suppression of antigen-specific adaptive immunity by IL-37 via induction of tolerogenic dendritic cells, Proc. Natl. Acad. Sci. U. S. A. 111 (42) (2014) 15178–15183.
[86] H. Fujita, Y. Inoue, K. Seto, N. Komitsu, M. Aihara, Interleukin-37 is elevated in subjects with atopic dermatitis, J. Dermatol. Sci. 69 (2) (2013) 173–175.
[87] D. Ghosh, L. Ding, U. Sivaprasad, E. Geh, J. Biagini Myers, J.A. Bernstein, G.K. Khurana Hershey, T.B. Mersha, Multiple transcriptome data analysis reveals biologically relevant atopic dermatitis signature genes and pathways, PLoS One 10 (12) (2015) e0144316.
[88] F. Grabherr, C. Grander, T.E. Adolph, V. Wieser, L. Mayr, B. Enrich, S. Macheiner, M. Sangineto, A. Reiter, A. Viveiros, H. Zoller, P. Bufler, A.R. Moschen, C.A. Dinarello, H. Tilg, Ethanol-mediated suppression of IL-37 licenses alcoholic liver disease, Liver Int. 38 (6) (2018) 1095–1101.
[89] J. Liu, J. Lin, S. He, C. Wu, B. Wang, J. Liu, Y. Duan, T. Liu, S. Shan, K. Yang, N. Dong, Q. Ji, K. Huang, D. Li, Transgenic overexpression of IL-37 protects against atherosclerosis and strengthens plaque stability, Cell. Physiol. Biochem. 45 (3) (2018) 1034–1050.
[90] L. Song, F. Qiu, Y. Fan, F. Ding, H. Liu, Q. Shu, W. Liu, X. Li, Glucocorticoid regulates interleukin-37 in systemic lupus erythematosus, J. Clin. Immunol. 33 (1) (2013) 111–117.
[91] G.C. Wu, H.M. Li, J.B. Wang, R.X. Leng, D.G. Wang, D.Q. Ye, Elevated plasma interleukin-37 levels in systemic lupus erythematosus patients, Lupus 25 (12) (2016) 1377–1380.
[92] M.G. Tawfik, S.I. Nasef, H.H. Omar, M.S. Ghaly, Serum Interleukin-37: a new player in Lupus Nephritis? Int. J. Rheum. Dis. 20 (8) (2017) 996–1001.
[93] L. Ye, L. Ji, Z. Wen, Y. Zhou, D. Hu, Y. Li, T. Yu, B. Chen, J. Zhang, L. Ding, J. Du, Z. Huang, IL-37 inhibits the production of inflammatory cytokines in peripheral blood mononuclear cells of patients with systemic lupus erythematosus: its correlation with disease activity, J. Transl. Med. 12 (2014) 69.
[94] W. Kaabachi, O. Kacem, R. Belhaj, A. Hamzaoui, K. Hamzaoui, Interleukin-37 in endometriosis, Immunol. Lett. 185 (2017) 52–55.
[95] M. Feng, M. Kang, F. He, Z. Xiao, Z. Liu, H. Yao, J. Wu, Plasma interleukin-37 is increased and inhibits the production of inflammatory cytokines in peripheral blood mononuclear cells in systemic juvenile idiopathic arthritis patients, J. Transl. Med. 16 (1) (2018) 277.
[96] R.M. Ruggeri, M. Cristani, T.M. Vicchio, A. Alibrandi, S. Giovinazzo, A. Saija, A. Campenni, F. Trimarchi, S. Gangemi, Increased serum interleukin-37 (IL-37) levels correlate with oxidative stress parameters in Hashimoto's thyroiditis, J. Endocrinol. Invest. 42 (2) (2018) 199–205.
[97] H. Chi, D. Liu, Y. Sun, Q. Hu, H. Liu, X. Cheng, J. Ye, H. Shi, Y. Yin, M. Liu, X. Wu, Z. Zhou, J. Teng, C. Yang, Y. Su, Interleukin-37 is increased in adult-onset Still's disease and associated with disease activity, Arthritis Res. Ther. 20 (1) (2018) 54.
[98] W. Liuqing, X. Liping, S. Hui, L. Jing, Elevated IL-37, IL-18 and IL-18BP serum concentrations in patients with primary Sjogren's syndrome, J. Investig. Med. 65 (3) (2017) 717–721.
[99] L. Liu, Y. Xue, Y. Zhu, D. Xuan, X. Yang, M. Liang, J. Wang, X. Zhu, J. Zhang, H. Zou, Interleukin 37 limits monosodium urate crystal-induced innate immune responses in human and murine models of gout, Arthritis Res. Ther. 18 (1) (2016) 268.
[100] C. Li, P. Zhao, X. Sun, Y. Che, Y. Jiang, Elevated levels of cerebrospinal fluid and plasma interleukin-37 in patients with Guillain-Barre syndrome, Mediators Inflamm. 2013 (2013) 639712.
[101] F. Zhou, C.L. Zhu, Z.L. Niu, F.X. Xu, H. Song, X.H. Liu, Influenza A virus inhibits influenza virus replication by inducing IL-37, J. Clin. Lab. Anal. (2018) e22638.
[102] H. Imaeda, K. Takahashi, T. Fujimoto, E. Kasumi, H. Ban, S. Bamba, H. Sonoda, T. Shimizu, Y. Fujiyama, A. Andoh, Epithelial expression of interleukin-37b in inflammatory bowel disease, Clin. Exp. Immunol. 172 (3) (2013) 410–416.
[103] B. Zhao, S. Zhang, W. Chen, R. Zhang, R. Jiang, R. Zhang, L. Chen, Elevated interleukin 37 expression associated with disease activity in HLA-B27 associated anterior uveitis and idiopathic anterior uveitis, Curr. Mol. Med. 17 (7) (2018) 460–467.
[104] M. Zhao, Y. Hu, Y. Yu, Q. Lin, J. Yang, S.B. Su, G.T. Xu, T. Yang, Involvement of IL-37 in the pathogenesis of proliferative diabetic retinopathy, Invest. Ophthalmol. Vis. Sci. 57 (7) (2016) 2955–2962.
[105] Y. Li, Z. Wang, T. Yu, B. Chen, J. Zhang, K. Huang, Z. Huang, Increased expression of IL-37 in patients with Graves' disease and its contribution to suppression of proinflammatory cytokines production in peripheral blood mononuclear cells, PLoS One 9 (9) (2014) e107183.
[106] J.L. Zhang, X.Y. Song, Y.Y. Chen, T.H.A. Nguyen, J.Y. Zhang, S.S. Bao, Y.Y. Zhang, Novel inflammatory cytokines (IL-36, 37, 38) in the aqueous humor from patients with chronic primary angle closure glaucoma, Int. Immunopharmacol. 71 (2019) 164–168.
[107] Z. Huang, C. Gao, X. Chi, Y.W. Hu, L. Zheng, T. Zeng, Q. Wang, IL-37 expression is upregulated in patients with tuberculosis and induces macrophages towards an M2-like phenotype, Scand. J. Immunol. 82 (4) (2015) 370–379.
[108] J.F. Hojen, T.A. Rasmussen, K.L. Andersen, A.A. Winckelmann, R.R. Laursen, J.D. Gunst, H.J. Moller, M. Fujita, L. Ostergaard, O.S. Sogaard, C.A. Dinarello,

M. Tolstrup, Interleukin-37 expression is increased in chronic HIV-1-infected individuals and is associated with inflammation and the size of the total viral reservoir, Mol. Med. 21 (2015) 337–345.
[109] B. Chen, K. Huang, L. Ye, Y. Li, J. Zhang, J. Zhang, X. Fan, X. Liu, L. Li, J. Sun, J. Du, Z. Huang, Interleukin-37 is increased in ankylosing spondylitis patients and associated with disease activity, J. Transl. Med. 13 (2015) 36.
[110] M. Farrokhi, A. Rezaei, A. Amani-Beni, M. Etemadifar, E. Kouchaki, A. Zahedi, Increased serum level of IL-37 in patients with multiple sclerosis and neuromyelitis optica, Acta Neurol. Belg. 115 (4) (2015) 609–614.
[111] M. Saresella, F. Piancone, I. Marventano, M. Zoppis, A. Hernis, M. Zanette, D. Trabattoni, M. Chiappedi, A. Ghezzo, M.P. Canevini, F. la Rosa, S. Esposito, M. Clerici, Multiple inflammasome complexes are activated in autistic spectrum disorders, Brain Behav. Immun. 57 (2016) 125–133.
[112] A.E. Alagbe, A.S. Justo Junior, L.P. Ruas, W.V. Tonasse, R.M. Santana, T.H.C. Batista, I.F. Domingos, A.S. Araujo, M.A.C. Bezerra, M.N.N. Santos, M. Blotta, Interleukin-27 and interleukin-37 are elevated in sickle cell anemia patients and inhibit in vitro secretion of interleukin-8 in neutrophils and monocytes, Cytokine 107 (2018) 85–92.
[113] Y.C. Wang, G.P. Weng, J.P. Liu, L. Li, Q.H. Cheng, Elevated serum IL-37 concentrations in patients with sepsis, Medicine (Baltimore) 98 (10) (2019) e14756.
[114] M. Sehat, R. Talaei, E. Dadgostar, H. Nikoueinejad, H. Akbari, Evaluating serum levels of IL-33, IL-36, IL-37 and gene expression of IL-37 in patients with psoriasis vulgaris, Iran. J. Allergy Asthma Immunol. 17 (2) (2018) 179–187.
[115] Z. Ye, C. Wang, A. Kijlstra, X. Zhou, P. Yang, A possible role for interleukin 37 in the pathogenesis of Behcet's disease, Curr. Mol. Med. 14 (4) (2014) 535–542.
[116] E. Bouali, W. Kaabachi, A. Hamzaoui, K. Hamzaoui, Interleukin-37 expression is decreased in Behcet's disease and is associated with inflammation, Immunol. Lett. 167 (2) (2015) 87–94.
[117] S. Ozguclu, T. Duman, F.S.O. Ates, O. Kucuksahin, S. Colak, U. Olmez, Serum interleukin-37 level and interleukin-37 gene polymorphism in patients with Behcet disease, Clin. Rheumatol. 38 (2) (2018) 495–502.
[118] J.F. Jiang, S.S. Xiao, M. Xue, Decreased expression of interleukin-37 in the ectopic and eutopic endometria of patients with adenomyosis, Gynecol. Endocrinol. 34 (1) (2018) 83–86.
[119] Z. Ye, C. Wang, J. Tang, Y. Zhou, L. Bai, Y. Liu, A. Kijlstra, P. Yang, Decreased interleukin-37 expression in Vogt-Koyanagi-Harada disease and upregulation following immunosuppressive treatment, J. Interferon Cytokine Res. 35 (4) (2015) 265–272.

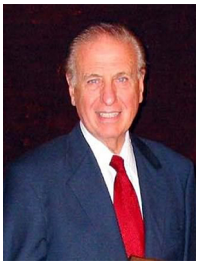
Zhaohao Huang earned his M.B. at the medical school of Nanchang University. Now he is a post-graduate student at Zhongshan ophthalmic center, Sun yat-sen university. His research focused mainly on immunology.

Lihui Xie earned his M.B. at the medical school of Nanchang University. Now he is a post-graduate student at Zhongshan ophthalmic center, Sun yat-sen university. His research focused mainly on immunology.

He Li earned his M.B. at the medical school of Jinan University. Now he is a post-graduate student at Zhongshan ophthalmic center, Sun yat-sen university. His research focused mainly on immunomodulation.



Xiuxing Liu earned his M.B. at the medical school of Nanchang University. Now he is a post-graduate student at Zhongshan ophthalmic center, Sun yat-sen university. His research focused mainly on immunology.



Dr. Joseph A. Bellanti is Director of the International Center for Interdisciplinary Studies of Immunology (ICISI) at Georgetown University Medical Center and Professor of Pediatrics and Microbiology-Immunology, (Emeritus) at Georgetown University School of Medicine, Washington, DC. Dr. Joseph A. Bellanti, a native of Buffalo New York, received his M.D. degree from the University of Buffalo in 1958. Following completion of a residency at the Children's Hospital of Buffalo in 1961, he was accepted into a National Institutes of Health-supported postdoctoral fellowship in a developmental immunology training program at the University of Florida in 1961 under the direction of Richard T. Smith, MD, a pioneering pediatric immunologist and disciple of Robert A. Good, MD (1961-62) and later continued his postdoctoral studies as a research virologist at Walter Reed Army Institute of Research (WRAIR), Washington, D.C. (1962-65), where among his many research contributions with his colleagues was the seminal description of the of secretory IgA antiviral principle of respiratory secretions. In 1963, he joined the faculty of Georgetown University School of Medicine as Assistant Professor of Pediatrics and Microbiology, where he rose to his current position of Professor of Pediatrics and Microbiology – Immunology in 1970.

Song Guo Zheng, he earned his M.D. at Anhui Medical University, M.S. at Fudan University Shanghai Medical School, and PhD at French National Center for Scientific Research and University of Orleans. He did his postdr studies at UCLA and University of Southern California (USC). He was appointed as Assistant Professor at USC in 2004 and Associate Professor at USC in 2010 and has been a director of Immune Regulation and Tolerance Lab at USC since 2004. He served as Professor of Medicine (tenured) and Director of Autoimmunity Research Center at Penn State University Hershey College of Medicine between 2013 and 2019. He has been appointed as Ronald L. Whisler Chair in Rheumatology and Immunology, Professor of Internal Medicine (tenured), Director of Rheumatology and Immunology Research at the Ohio State University Wexner Medical Center and College of Medicine since 2019. Dr. Zheng and his colleagues discover TGF-β-induced regulatory T cells and focuses on the development and function of regulatory and effector T cells in autoimmunity.

Wenru Su earned his M.B. at Bengbu medical school, M.D. and PhD at Zhongshan ophthalmic center, Sun yat-sen university, he did his postdr studies at University of Southern California (USC). He was appointed as Assistant Professor in 2012, and Associate Professor, doctoral supervisor in 2015. He has devoted himself into diagnosis and treatment of various ocular immune diseases (such as uveitis) for more than 10 years. He focused on the the pathogenesis of autoimmune and allergic diseases, especially for Ocular diseases.