

REVIEW

The role of interleukin-1 β in the immune response to contact allergens

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Abstract

Interleukin-1 β (IL-1 β) is an important pro-inflammatory cytokine that has an effect on almost every cell lineage in the body. By blocking IL-1 β and investigating the IL-1 β signaling pathway, several studies have demonstrated a central role of IL-1 β in the response to contact allergens. This review summarizes the current literature regarding the basic immunological mechanisms mediated by IL-1 β in the different phases of allergic contact dermatitis (ACD) and highlights potential IL-1 β -targeted treatment options, which in the future may be relevant in the treatment of patients with ACD. This review is based primarily on studies using various mouse models and human in vitro studies, since clinical studies on the effect of IL-1 β in ACD are lacking.

KEYWORDS

allergic contact dermatitis, immunology, interleukin-1 β , T cells

1 | INTRODUCTION

Allergic contact dermatitis (ACD) is a T cell-mediated immune disease. The immune response induced by contact allergens is divided into two phases (1) the sensitization phase and (2) the elicitation phase. Interleukin-1 β (IL-1 β) is a central cytokine in both phases. Thus numerous studies have demonstrated that defects in the IL-1 β signaling pathway or blocking of IL-1 β results in decreased responses to contact allergens.¹⁻⁵ IL-1 β is involved in many different biological functions including production of various cytokines and chemokines by immune and nonimmune cells, upregulation of MHC-II on Langerhans cells (LCs), and initiation of the migration of LCs from the epidermis to the draining lymph nodes.^{6,7} This review will explore the properties, biological function, and immunological role of IL-1 β in ACD.

2 | IL-1 β AND THE INTERLEUKIN-1 RECEPTOR

2.1 | Structure and production of IL-1 β

IL-1 β is coded by the *IL1B* gene on chromosome 2 in humans.⁸ IL-1 β composed of 12 antiparallel β strands that form a network of

hydrogen bonds, and the overall folding of the β strands resembles a triangular pyramid.⁹ IL-1 β is part of the IL-1 family, which consists of 11 cytokines so far. Seven of the cytokines in the family act as agonists (IL-1 α , IL-1 β , IL-18, IL-33, IL-36 α , IL-36 β , and IL-36 γ), whereas the remaining four (IL-1Ra, IL-36Ra, IL-37, and IL-38) function as antagonists on the interleukin-1 receptor type 1 (IL-1RI).^{10,11}

Various cell types can produce IL-1 β , including dendritic cells, keratinocytes, macrophages, fibroblasts, epithelial cells, and endothelial cells.¹² In the skin, the main cellular sources under physiological conditions of IL-1 β in the epidermis are LCs and keratinocytes, whereas macrophages and dermal dendritic cells are the main IL-1 β sources in the dermis.⁴

IL-1 β is synthesized as a premature cytokine termed pro-IL-1 β .¹³⁻¹⁶ The synthesis of the functional mature, active IL-1 β is highly regulated and can be subdivided into two stages, namely priming (signal one) and activation (signal two) (Figure 1).¹⁷ During priming, a cell is stimulated through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).^{18,19} Activation of PRRs leads to signaling via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway that upregulates the expression of pro-

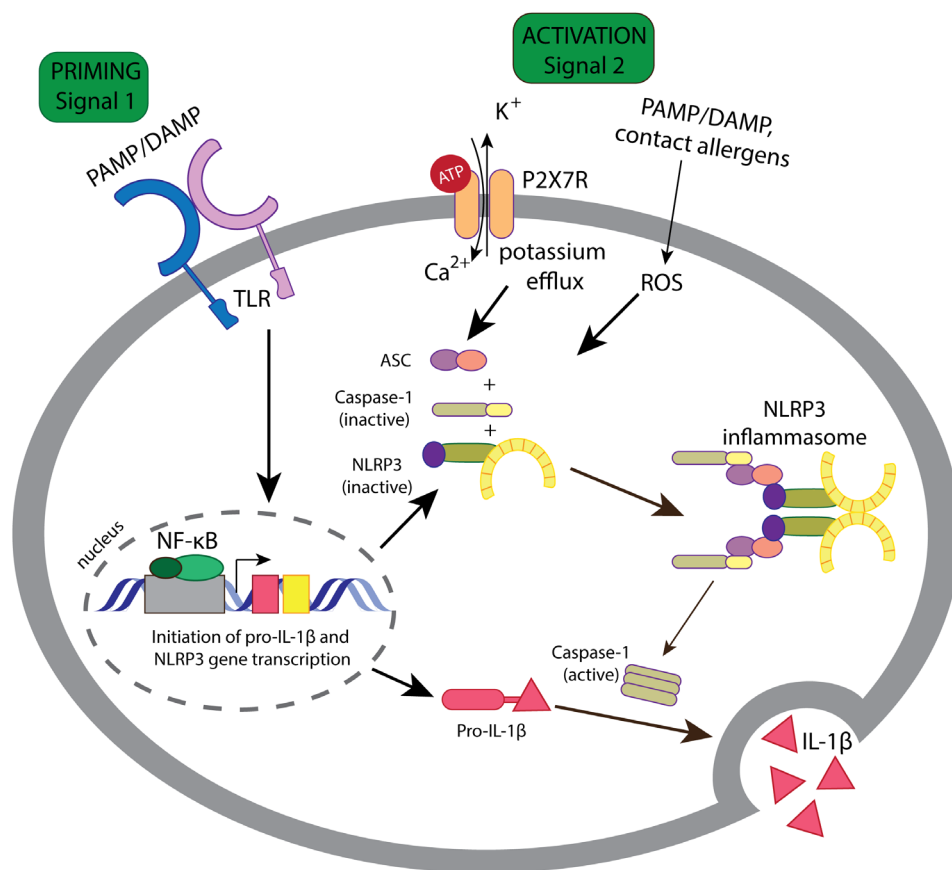


FIGURE 1 Production of IL-1 β . Priming: Pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) produced from contact allergen application on skin activate pattern recognition receptors (PRR) which initiates pro-IL-1 β and NOD-like receptor family pyrin domain containing 3 (NLRP3) gene transcription. Activation: The NLRP3 inflammasome consists of the NLRP3 receptor, pro-caspase 1, and an adaptor protein called apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) that couples the two. Formation of the NLRP3 inflammasome can be triggered by potassium efflux, extracellular ATP, and radical oxygen species (ROS). Activation of NLRP3 lead to cleavage of pro-caspase-1 to its active form. The active form of caspase-1 then cleaves pro-IL-1 β to its active, mature form

IL-1 β and NOD-like receptor protein 3 (NLRP3).²⁰ NLRP3 recruits the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD)) that links NLRP3 with the pro-caspase-1 forming the NLRP3 inflammasome.^{21,22} In the second stages, NLRP3 is activated through different stimuli such as reactive oxygen species (ROS), extracellular ATP, reduced cytosolic potassium levels, sodium urate, and contact allergens.^{17,18} Activation of NLRP3 leads to cleavage of pro-caspase-1 to its active form. The active form of caspase-1 then cleaves pro-IL-1 β to its active, mature form. Furthermore, production and activation of pro-IL-1 β might also be induced in an autocrine manner through IL-1 β stimulation of the IL-1RI.²³⁻²⁶

2.2 | The interleukin-1 receptor and intracellular signaling

The interleukin-1 receptor (IL-1R) family consists of 10 structurally related members, where IL-1RI and IL-1RII are of particular interest and significance to ACD.²⁷ IL-1RI and IL-1RII contain three extracellular immunoglobulin domains (Figure 2) and can bind a variety of different cytokines from the IL-1 family, including IL-1 α , IL-1 β , and IL-1Ra. IL-1RI contains an intracellular domain known as the Toll-like/IL-1R (TIR) domain, whereas IL-1RII lacks this domain (Figure 2).

The formation of a binary complex is a key step in signal initiation. When IL-1 β binds to its primary receptor (IL-1RI) a binary IL-1 β :IL-1RI

complex is formed. The binary complex creates a composite surface that allows the recruitment of the co-receptor interleukin-1 receptor accessory protein (IL-1RAcP) required for signal induction (Figure 2).²⁸ Formation of the ternary IL-1 β :IL-1RI:IL-1RAcP complex induces the juxtaposition and thereby activation of the cytoplasmic TIR domains of IL-1RI and IL-1RAcP. The activated TIR domains recruit intracellular signaling factors and initiate the signaling cascade. The formation of a binary and ternary complex is similar for the decoy receptor IL-1RII, but as this receptor lacks the cytoplasmic TIR domain, a nonfunctional ternary complex is formed.²⁹ Furthermore, the cytokine interleukin-1 receptor antagonist (IL-1Ra), belonging to the IL-1 family, binds to IL-1RI forming an inhibitory IL-Ra:IL-1RI binary complex that fails to form ternary complexes with IL-1RAcP, thereby exerting its antagonistic effect (Figure 2).³⁰

Formation of ternary IL-1 β :IL-1RI:IL-1RAcP complexes initiates intracellular signaling transduction. The TIR domains recruit several intracellular adaptor molecules such as myeloid differentiation factor 88 (MYD88), IL-1R-associated kinases (IRAK) and tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6). Through a complex sequence of phosphorylations and ubiquitinations, activation of downstream signaling molecules such as NF- κ B, activator protein 1 (AP-1) and mitogen-activated protein kinase (MAPK), including p38 mitogen-activated protein kinase (p38), c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK), occurs.^{31,32} This results in the activation of genes coding for inflammatory mediators such as IL-6, IL-8, monocyte chemoattractant protein-1, cyclooxygenase-2, IL-17A, interferon gamma (IFN γ), nuclear factor of kappa light

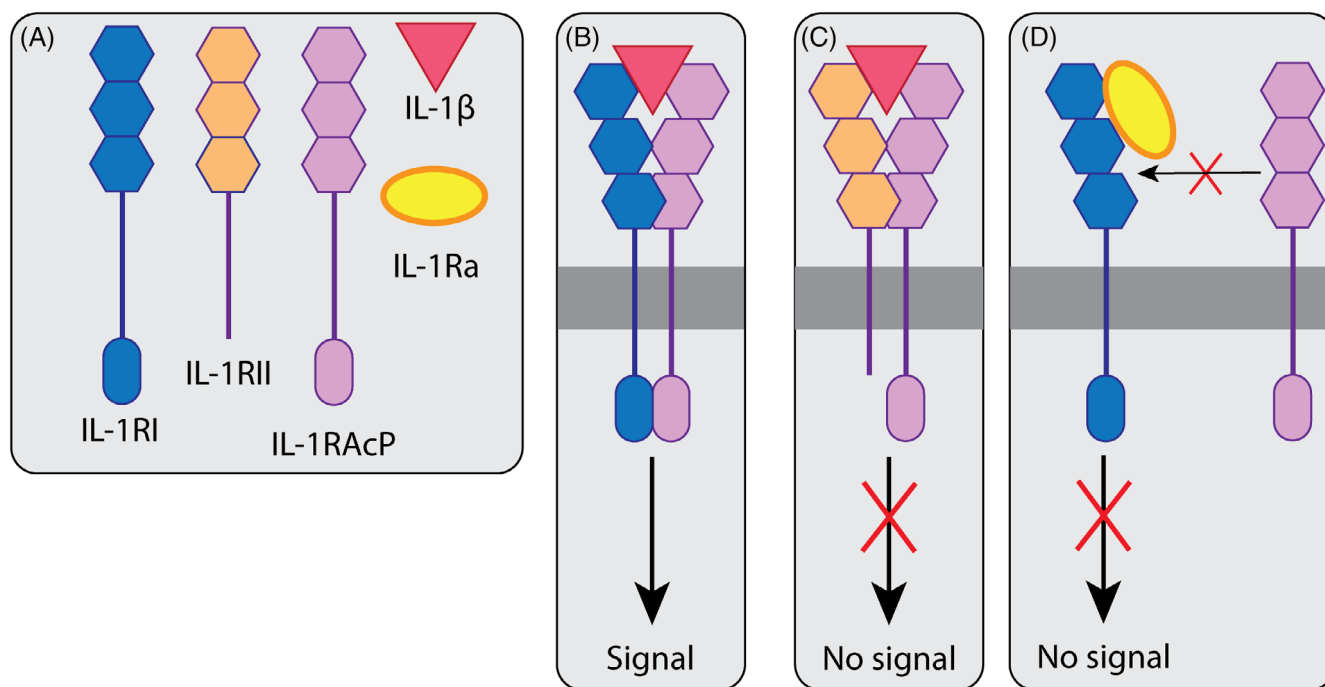


FIGURE 2 IL-1 receptor subtypes. Binding of IL-1 β and intracellular signaling is mediated via the surface receptor IL-1RI. A, IL-1RI, interleukin-1 receptor type 1, IL-1RII, interleukin-1 receptor type 2, IL-1RAcP, interleukin-1 receptor accessory protein, IL-1Ra, interleukin-1 receptor antagonist. B, Formation of the ternary IL-1 β :IL-1RI:IL-1RAcP complex activates the cytoplasmic Toll-like/IL-1R (TIR) domains of IL-1RI and IL-1RAcP and leads to downstream signaling. C, The receptor IL-1RII lacks a cytoplasmic TIR domain, and formation of the ternary IL-1 β :IL-1RII:IL-1RAcP complex is nonfunctional. D, IL-1Ra inhibits the formation of a ternary complex

polypeptide gene enhancer in B-cells inhibitor, alpha ($\text{I}\kappa\text{B}\alpha$), IL-1 α , IL-1 β , mitogen-activated protein kinase phosphatase 1, type 2 phospholipase A, and inducible nitric oxide synthase (iNOS).³³

2.3 | Mechanisms of IL-1 β secretion

The secretion of IL-1 β does not follow the classical secretory pathway for proteins. Different nonclassical secretory pathways for IL-1 β release have been proposed, which are the following: exocytosis of secretory lysosomes,³⁴ shedding of plasma membrane microvesicles,³⁵ exocytosis of exosomes,³⁶ or by export through the plasma membrane using specialized transporters.³⁷ In addition, it has also been shown that the cytoplasmic protein gasdermin D plays a role in IL-1 β release. Gasdermin D can induce pyroptosis, which leads to a passive release of cytosolic IL-1 β , but can also mediate active secretion of IL-1 β .³⁸

3 | THE ROLE OF IL-1 β IN ALLERGIC CONTACT DERMATITIS

3.1 | Induction of IL-1 β by contact allergens

The NLRP3 inflammasome and its importance for IL-1 β in ACD have been investigated by several groups. Watanabe et al used an ACD model in mice deficient of IL-1RI, ASC, or NLRP3.⁴ Ear swelling was decreased in the early phase of elicitation in IL-1RI-, ASC-, and

NLRP3-deficient mice compared to wild-type (WT) mice sensitized and challenged with trinitrochlorobenzene (TNCB). In the late phase of elicitation, only the IL-1RI-deficient mice had reduced ear swelling compared to WT mice. In line with this, other studies have found that the immunoreceptor tyrosine-based activation motif (ITAM)-bearing adaptor molecules DNAX-activating protein of 12 kDa (DAP12), the adaptor protein caspase recruitment domain-containing protein 9 (CARD9), ASC, and NLRP3 all are required to raise a response upon allergen challenge.^{1,39} Watanabe et al also found that tolerance development depends on reduced IL-1 β signaling rather than on the antigenic properties of a contact allergen.² They showed that WT mice injected with cells from dinitrofluorobenzene (DNFB)-primed, IL-1R- or ASC-deficient mice had significantly decreased ear swelling when challenged with DNFB, suggesting that tolerance develops in the absence of inflammasome-mediated IL-1 β activation.² Antonopoulos et al also explored the role of the inflammasome and found decreased ear swelling in caspase-1-deficient BALB/c mice that were sensitized and challenged with DNFB or oxazolone compared to WT mice.⁴⁰

Several other intracellular signaling molecules that are involved in the IL-1 β signaling pathway have been studied in relation to contact allergy. One study found that exposure to nickel increased the expression of IL-1 β through MYD88-dependent signaling.⁵ The role of MYD88 and IL-1RI signaling was further explored by Naik et al and Klekotka et al, who showed decreased ear swelling and IL-17A levels in both MYD88- and IL-1RI-deficient mice.^{41,42} Of interest, Klekotka et al found that chimeras deficient in both MYD88 and TIR-domain-containing adapter-inducing interferon- β (TRIF) had decreased levels

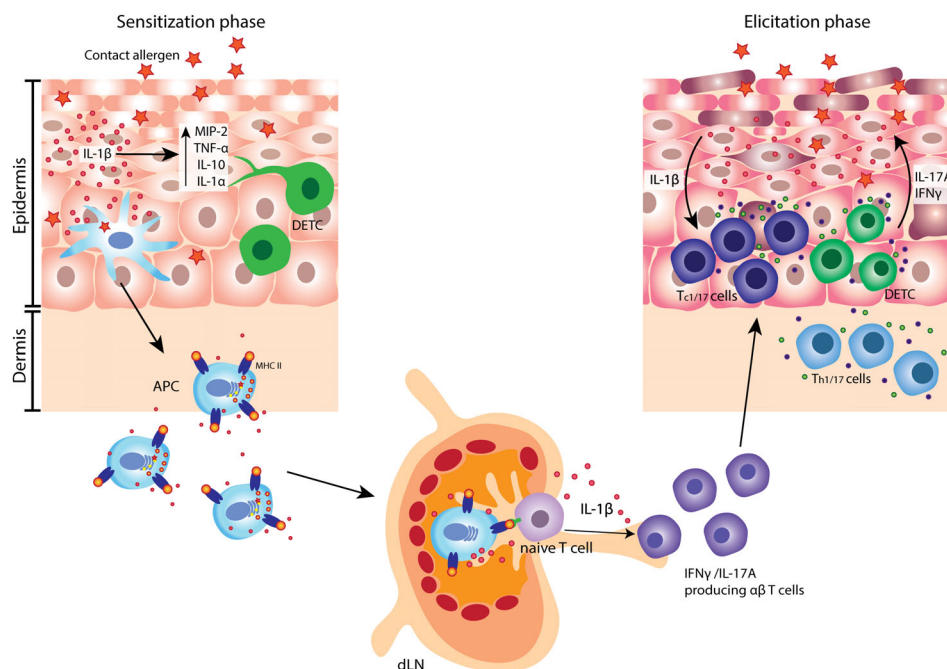


FIGURE 3 The role of IL-1 β in relation to allergic contact dermatitis (ACD). In the sensitization phase of ACD, contact allergen mediated tissue damage lead to increased production of IL-1 β by keratinocytes and APC. IL-1 β increases or induces the expression of other inflammatory cytokines. Antigen presenting cells (APC) and IL-1 β initiates the activation and differentiation of naïve T cells into effector or memory T cells. Upon elicitation memory T cells residing in the skin are activated. Large amounts of IL-1 β are produced and recruitment of T cells from the circulation occurs. The activated T cells mediate inflammation through IFN γ and IL-17A which triggers a sustained production of IL-1 β from keratinocytes and APC

of both IL-17A and IFN γ in the skin.⁴² In line with this, Yasukawa et al found that mice deficient in MYD88 and CARD9 failed to develop ACD, and that T cells from sensitized WT mice did elicit ACD after transfer to naïve MYD88- or CARD9-deficient mice.³⁹ These results indicated that MYD88 and CARD9 are required during the sensitization phase. The role of the P2X $_7$ receptor, which senses extracellular ATP in NLRP3 inflammasome and IL-1 β activation in ACD was explored by Weber et al. They found that mice deficient in P2X $_7$ had abrogated responses toward allergens and that bone marrow-derived cells of P2X $_7$ -deficient mice failed to process and release mature IL-1 β . However, ACD was restored when the mice were injected with rIL-1 β before allergenic stimulation, suggesting an important role for the P2X $_7$ receptor in IL-1 β activation.³ These studies indicate that many contact allergens have the ability to activate the NLRP3 inflammasome and thereby induce the production of IL-1 β .

3.2 | Cellular sources of contact allergen-induced IL-1 β

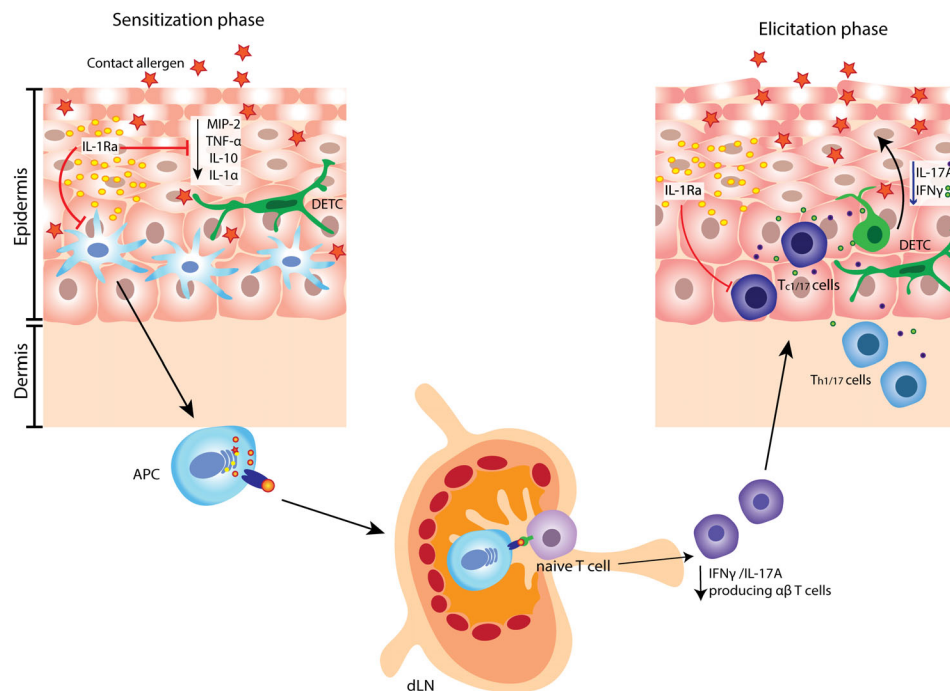
Several *in vivo* mouse models have explored the cellular sources of IL-1 β in ACD. Enk and Katz showed that IL-1 β mRNA levels rapidly increased after exposure of the skin of nonsensitized BALB/c mice to the contact allergen trinitrochlorobenzene (or TNCB).⁴³ They found that IL-1 β was the first cytokine to be upregulated and that it could be detected already 15 minutes after TNCB application. In the same study, depletion of LCs resulted in decreased levels of IL-1 β , whereas depletion of CD4 $^{+}$ and CD8 $^{+}$ T cells did not affected the induction of IL-1 β . This indicated that epidermal LCs were the primary source of IL-1 β in the sensitization phase. The rapid upregulation of IL-1 β mRNA and protein levels was confirmed in C57BL/6 mice, where increased levels of IL-1 β were seen even 48 hours after exposure to the contact allergen.⁴⁴

Keratinocytes are known for their strong structural barrier function but their role in mediating an immune response is also of keen interest. Enk et al studied the effects of IL-1 β on cytokine production in keratinocytes and found that IL-1 β treatment increased MIP-2, TNF- α , IL-10, and IL-1 α mRNA levels (Figure 3).⁴⁵ Watanabe et al showed that primary human keratinocytes contain the necessary molecular components to form and activate the NLRP3 inflammasome upon stimulation with TNCB, a chemical irritant (SDS) or ultraviolet B light.⁴ Thus keratinocytes can produce and secrete IL-1 β independently of classical immune cells.⁴ Keratinocytes from ASC-deficient mice failed to secrete IL-1 β upon exposure to TNCB, supporting the important role of the NLRP3 inflammasome in IL-1 β secretion.⁴ In line with this, IL-1 β secretion and activation were blocked when exposing primary human keratinocytes to TNCB in the presence of a specific caspase-1 inhibitor. Zepter et al found that human keratinocytes had the ability to produce pro-IL-1 β and to process it to mature IL-1 β by upregulating caspase-1 activity when stimulated with the contact allergen urushiol.⁴⁶ As Watanabe et al, they also found that a caspase inhibitor inhibited IL-1 β secretion. We have shown that mouse keratinocytes stimulated with dinitrobenzene sulfonic acid (DNBS) secrete IL-1 β and that an additive effect was seen if stimulation with DNBS was combined with IL-17A and/or IFN γ .^{44,47} Taken together, these studies showed that LCs and keratinocytes are important sources of IL-1 β in both humans and mice.

3.3 | The role of IL-1 β in activation and migration of antigen-presenting cells

LCs are antigen presenting cells (APCs) in the skin and are important for regulating T cell activation. The role of IL-1 β in activation and enhancing the function of APC in the skin has been studied in numerous studies.^{39,40,45,48} Enk et al showed that LCs derived from IL-1 β -treated skin were activated with increased MHC class II expression and that they were

FIGURE 4 The inhibitory effects of IL-1Ra. The administration of IL-1Ra during sensitization leads to decreased APC migration from the skin, decreased expression of MHC Class II molecules (MHC-II) and decreased levels of IL-1 β and its downstream cytokines. IL-1Ra thereby dampens the differentiation and activation of naïve T cells. Inhibition and decreased recruitment of T cells from the skin and circulation occurs if IL-1Ra is administered during challenge, which ameliorates the allergic contact dermatitis (ACD) response



far more potent in inducing T cell proliferation than LCs derived from untreated or TNCB-treated skin (Figure 3).⁴⁵ Another study found that IL-1 β was required for normal LC migration and that a caspase-1 inhibitor inhibited LC migration.⁴⁰ The morphological changes induced by treatment of LC with IL-1 β have been investigated by immunofluorescence microscopy. Enk et al found that LCs in epidermal ear sheets treated with IL-1 β were enlarged in size but decreased in numbers to less than 50% compared to ear sheets treated with PBS.⁴⁵ Accordingly, Shornick et al demonstrated that the morphology of LCs in skin treated with IL-1 β was similar to the morphology of LCs in mice sensitized with 1% TNCB, supporting that IL-1 β is sufficient for local LC activation and induction of LC migration.⁴⁸ Cumberbatch et al found a markedly decreased accumulation of DC in the dLN of mice sensitized with oxazolone when they were pre-treated with anti-IL-1 β antibody (Figure 4).⁴⁹ In line with this, Shornick et al found impaired delivery of antigen to the lymph nodes in IL-1 β -deficient mice.⁴⁸ In correlation, LC migration was impaired in caspase-1-deficient after they had been challenged with 0.5% DNFB. Of interest, after injection with IL-1 β , the LCs from caspase-1-deficient mice were as efficient to migrate as the LCs from the WT mice.⁴⁰ An absence of lymphocyte proliferative response was seen in IL-1 β -deficient mice when stimulated with a contact allergen, and the ear swelling was decreased when they were sensitized and challenged with TNCB (Figure 4).⁴⁸ However, the response could be restored by i.d. injection of rIL-1 β .⁵⁰

Together, these studies support a central role of IL-1 β in APC activation and migration.

3.4 | The role of IL-1 β in the recruitment of inflammatory cells to skin exposed to contact allergen

The inflammatory infiltrate in ACD contains predominantly lymphocytes and other mononuclear cells. Hematoxylin and eosin

(HE) staining ear sheets showed no detectable inflammatory infiltrate in IL-1 β -deficient mice sensitized with a contact allergen, but if these mice were administered rIL-1 β prior to sensitization, an inflammatory infiltrate could be seen (Figures 3 and 4).⁵⁰ Kondo et al stained ear sheets 48 hours after challenge with DNFB, and showed that i.d. administration of 10 μ g IL-1Ra right before the challenge decreased the edema and inflammatory infiltration in both the dermis and epidermis compared to mice injected with PBS.⁵¹ Watanabe et al showed less edema and vasodilation 5 hours after challenge in stained ear sheets from ASC-deficient sensitized mice compared to their WT littermates,⁴ whereas Yasukawa et al showed less edema and mononuclear cell infiltration in MYD88- and CAD9-deficient mice.³⁹ Weber et al showed that ear sheets from mice deficient in P2X₇ also had lesser edema and inflammatory infiltrates on HE stain.³ Taken together, this shows that the IL-1 β pathway plays a central role in the cellular infiltration and edema in ACD.

3.5 | The role of IL-1 β in allergen-induced T cell activation and differentiation

As described above, IL-1 β plays a critical role in the contact allergen-induced activation and migration of skin APC to the dLN, which is a critical step in the activation of naïve, allergen-specific T cells. Furthermore, IL-1 β seems to play a central role in T cell differentiation during the response to contact allergens. Naïve CD4⁺ T cells can differentiate into different subset of effector T cells including Th1, Th2, and Th17 cells. IL-1 β together with IL-6 stimulate the early stages of CD4⁺ T cell differentiation into Th17 cells, whereas IL-23 is important for the proliferation and maintenance of differentiated Th17 cells.⁵² T cells from mice lacking IL-1RI fail to produce IL-17 upon antigen

stimulation, indicating an important role of IL-1 β for Th17 maturation (Figure 4).⁵³ Accordingly, Naik et al found that the presence of IL-1 β during activation of T cells potentially increased their production of IL-17A.⁴¹ The levels of IL-17A and IFN γ were significantly impaired in stimulated T cells isolated from dLNs of sensitized mice deficient of MYD88 or CARD9.³⁹ Moreover, when naïve T cells were co-cultured with TNP-DC, known to induce IL-1 β secretion, an increase in IL-17A levels was seen for the T cells. However, the increase in IL-17A levels was abolished in MYD88- and IL-1R-deficient T cells, suggesting that the IL-1R-MYD88 signaling pathway play an important role in differentiation of Th17 cells.³⁹ In accordance, ASC-deficient mice had reduced levels of IL-6 and IL-12/IL-23 compared to WT mice, which supports the central role of IL-1 β in the differentiation of T cells into a Th1 and Th17 response.² Th17 cells mainly produce IL-17, IL-21, and IL-22, and they play important roles in the defense against pathogens.^{54–61} In addition to Th17 cells, both IL-17-producing CD8⁺ T cells and $\gamma\delta$ T cells can be found in the skin.^{41,44,47,62} It is important to note that IL-1 β is a contributor to several aspects of the expansion, effector function, tissue localization, and memory response of CD8⁺ T cells (Figure 3).⁶³

3.6 | Interplay between IL-1 β and epidermal resident T cells

In addition to playing a central role in the activation and differentiation of naïve allergen-specific T cells in the draining lymph nodes, IL-1 β affects various subsets of epidermal resident T cells. The majority of epidermal T cells found in the epidermis of naïve mice constitutes a subset of $\gamma\delta$ T cells termed dendritic epidermal T cells (DETCs).⁶⁴ We explored the role of IL-1 β on the production of IL-17A and IFN γ in DETCs. Purified DETCs from murine epidermis produced low amounts of IL-17A when they were treated with either IL-1 β , IL-23, or anti-CD3. Of interest, treatment with IL-1 β in combination with anti-CD3 was highly effective in inducing IL-17A and IFN γ in cultured DETCs.⁴⁴ These results indicated that the presence of IL-1 β increases the production of IL-17A and IFN γ during DETC activation. Furthermore, treatment of resting DETCs with IL-1 β induces a partial activation of the DETCs as seen by retraction of their dendritic processes. Conversely, DETCs maintain their dendritic morphology in the epidermis if IL-1Ra is added before allergen challenge.⁴⁴ These results indicate that IL-1 β provides the necessary signals to activate DETCs partially. Upon sensitization, epidermal-resident memory CD8⁺ T cells are formed locally in the skin areas exposed to the contact allergen.^{47,65,66} A dramatic increase in the level of IL-1 β at sites previously exposed to antigen compared to unexposed sites is seen upon challenge. This increase seems to be mediated by the epidermal-resident memory CD8⁺ T cells, as the increase is lacking in RAG-2 knockout mice.⁴⁷ Thus IL-1 β partially activate DETCs, and vice versa activated epidermal-resident memory CD8⁺ T induce the production of high amounts of IL-1 β .

3.7 | Human studies

The role of IL-1 β in ACD has been investigated intensively in murine *in vivo* models compared to human models. However, Mattii et al showed increased mRNA levels of IL-1 β and IL-1Ra in lesional and nonlesional skin from human subjects with ACD compared to healthy controls without ACD.⁶⁷ Schmidt et al could also show that patients with nickel allergy have distinctly localized memory responses to nickel at previously exposed skin sites in human subjects.⁴⁷ The levels of IL-1 β and IL-17A were increased at skin sites previously exposed to nickel upon re-exposure compared to skin sites without prior exposure.⁴⁷ Guéniche et al could also show an increase in IL-1 β levels *in vitro* when normal human keratinocytes were cultured with nickel.⁶⁸ Furthermore, Boehm et al showed an increase in epidermal IL-1 β levels by *in situ* hybridization in human subjects who were sensitive to the contact allergen urushiol.⁶⁹

The results from human studies are in accordance with the results from studies using murine models, indicating that similar immune mechanisms may take place in humans and mice.

4 | THE ROLE OF IL-1 β IN IRRITANT CONTACT DERMATITIS AND ATOPIC DERMATITIS

4.1 | Irritant contact dermatitis

Although irritant and allergic contact dermatitis share common clinical characteristics, the role of IL-1 β in irritant contact dermatitis (ICD) is conflicting. Some studies found no significant increase in levels of IL-1 β after stimulation with chemical irritants,^{70,71} whereas other studies have shown a similar increase in IL-1 β levels after allergenic or irritant stimulation.^{4,72} The role of IL-1 β in ICD compared to ACD is yet to be elucidated.

4.2 | Atopic dermatitis

Atopic dermatitis (AD) is considered a Th2 cell-mediated immune response.⁷³ However, several studies have suggested that IL-1 β may contribute to the skin inflammation seen in AD. Murine models resembling human AD have shown increased IL-1 β mRNA expression in local inflamed skin lesions,^{74,75} and a critical role of IL-1 β in the initiation and maintenance of skin inflammation.⁷⁶ In humans, transcripts of IL-1 β mRNA were significantly expressed in lesional skin of acute and chronic lesions in patients with AD.^{77–79} Another study showed a direct correlation between increasing levels of IL-1 β and AD severity.⁸⁰ Of interest, Bernard et al showed that IL-1 β might be an early key mediator for the acquisition of an AD phenotype through induction of thymic stromal lymphoprotein,⁸¹ and Junghans et al showed that epicutaneous application of ragweed or house dust mite antigen upregulated IL-1 β mRNA expression from the skin of AD patients

TABLE 1 Characteristics and summary of studies exploring the potential of targeting the IL-1 β pathway

Mouse strain	Contact allergen	Drug	Administration	Regimen	Effect (level of inhibition)	Reference
Inhibition of sensitization phase in murine in vivo studies						
BALB/c mice	3% TNCB	Anti-IL-1 β mAb	i.d.	250 μ g prior to sensitization	Ear thickness change in treatment group: 0.18 mm, compared to control group: 0.35 mm	Enk et al ⁴⁵ (1993)
BALB/c mice	0.5% DNFB	IL-1Ra	i.d.	10 μ g 5 h prior to sensitization	Ear thickness change in treatment group: 0.05 mm, compared to control group: 0.10 mm	Kondo et al ⁵¹ (1995)
BALB/c mice	0.5% DNFB	IL-1Ra	i.p.	15 mg twice daily for three consecutive days, starting 12 h before sensitization	Ear thickness change in treatment group: 0.09 mm, compared to control group: 0.18 mm	Watanabe et al ² (2008)
C57BL/6 mice	3% TNCB	IL-1Ra	i.v.	200 μ g on day five, three, and one before sensitization	Ear thickness change in treatment group: 0.04 mm, compared to control group: 0.13 mm	Weber et al ³ (2010)
Filaggrin-deficient flaky tail mice	10% NiCl ₂	IL-1Ra	i.p.	30 mg twice daily for 3 d. Starting one dose 16 h before sensitization, and the last dose being giving 8 h after NiCl ₂ application	Ear thickness in treatment group: 0.33 mm, compared to control group: 0.40 mm	Petersen et al ⁸³ (2019)
BALB/c mice	0.5% DNFB	Caspase-1 inhibitor	Topical	300 μ L of 400 μ M ac-YVAD-cmk 1 h before application of sensitizer and 0, 2, 4, 6, and 8 h after sensitization	Ear thickness change in treatment group: 0.07 mm, compared to control group: 0.12 mm	Antonopoulos et al ⁴⁰ (2001)
ASC-deficient mice	0.5% DNFB	Caspase-1 inhibitor	Topical	20 μ L of 0.2 mM zYVAD 30 min before sensitization on days 0, 1, and 2	Ear thickness change in treatment group: 0.03 mm, compared to control group: 0.18 mm	Watanabe et al ² (2008)
C57BL/6 mice	3% TNCB	P2X7 receptor antagonist	i.d.	50 μ L of 71.4 μ g/mL KN-62 4 h before sensitization	Ear thickness change in treatment group: 0.03 mm, compared to control group: 0.10 mm	Weber et al ³ (2010)
Inhibition of elicitation phase in murine in vivo studies						
BALB/c mice	0.2% DNFB	IL-1Ra	i.d.	Varying dose ranging from 10-100 μ g was injected 24, 12, 6, 3, 1, or 0 h before challenge	36%-43% decrease in ear swelling compared to control group	Kondo et al ⁵¹ (1995)
C57BL/6 mice	10% NiCl ₂	IL-1Ra	i.p.	2500 μ g twice daily both during sensitization and elicitation phase	Ear thickness in treatment group: 102%, compared to control group: 118%	Vennegaard et al ⁵ (2014)
Filaggrin-deficient flaky tail mice	10% NiCl ₂	IL-1Ra	i.p.	30 mg twice daily starting at 16 h before challenge	Ear thickness in treatment group: 0.37 mm, compared to control group: 0.42 mm	Petersen et al ⁸³ (2019)

Abbreviations: Ac-YVAD-cmk, acetyl-tyrosyl-valyl-alanyl-aspartyl-chloromethylketone caspase-1 inhibitor; DNFB, dinitrofluorobenzene; i.d., intradermal; i.p., intraperitoneal; i.v., intravenous; IL-1Ra, interleukin-1 receptor antagonist; KN-62, P2X₇ receptor antagonist; mAb, monoclonal antibody; NiCl₂, nickel chloride; Rhu IL-1R, recombinant human interleukin-1 receptor; s.c., subcutaneous; TNCB, trinitrochlorobenzene; zYVAD, benzoxycarbonyl-tyrosyl-valyl-alanyl-aspartyl caspase-1 inhibitor.

compared to healthy participants.⁸² Taken together these data might indicate that IL-1 β plays a role in the development, maintenance, and exacerbation of AD.

5 | POTENTIAL OF TARGETING THE IL-1 β PATHWAYS IN THE TREATMENT OF ALLERGIC CONTACT DERMATITIS

5.1 | Inhibition of the sensitization phase

Numerous studies have shown the effects of IL-1 β -targeted treatment in ameliorating ACD in mice (Table 1). Enk et al showed that an i.d. injection of 250 μ g anti-IL-1 β monoclonal antibodies (mAb) right before sensitization with 3% TNCB on the ears of naïve BALB/c mice inhibited allergen sensitization.⁴⁵ The mice were challenged 5 days later, and a clinically significant reduction in ear swelling, measured 24 hours after the challenge, was noted in the anti-IL-1 β mAb-treated group. Kondo et al found similar results using IL-1Ra instead of anti-IL-1 β mAb.⁵¹ They sensitized BALB/c mice with 0.5% DNFB on one ear and 5 days later, the contralateral ear was challenged with 0.2% DNFB. A dose of 10 μ g IL-1Ra was injected i.d. 5 hours before sensitization; this resulted in significant suppression of ear swelling measured 24 and 48 hours after challenge. Watanabe et al showed that BALB/c mice receiving IL-1Ra intraperitoneally (i.p.) for three consecutive days, starting 12 hours before sensitization with DNFB, had decreased ear swelling on day 5 upon challenge.² Weber et al conducted a study on C57BL/6 mice receiving 200 μ g of IL-1Ra intravenously (i.v.) on days 5, 3, and 1 before sensitization with 3% TNCB on the abdomen. On day 5 the mice were challenged with 1% TNCB on their ears dorsally, and the IL-1Ra-treated mice had decreased ear swelling.³ Likewise, administering 30 mg, i.p., of IL-1Ra twice daily during sensitization with nickel in filaggrin-deficient flaky tail mice resulted in a 25% reduction in IFN γ -producing CD8⁺ T cells within the dLN in addition to a reduced ear swelling upon nickel challenge.⁸³ Antonopoulos et al showed suppression of ACD by topical application of caspase-1 inhibitors before sensitization with 0.5% DNFB on the unshaved abdominal skin of BALB/c mice; 5 days later they challenged the mice with 0.25% DNFB on one ear and found statistically significant decreased ear swelling at 24 and 48 hours after challenge.⁴⁰ Watanabe et al have shown similar results with topical application of caspase-1 inhibitors before sensitization with DNFB, which led to decreased ear swelling measurements when mice were challenged at day 5 after sensitization.² Weber et al investigated the role of blocking the P2X₇ receptor, an important receptor in inflammasome activation, and they could see decreased ear swelling upon challenge 5 days after sensitization with TNCB.³

5.2 | Inhibition of the elicitation phase

The elicitation phase in ACD can also be inhibited by targeting the IL-1 β pathway (Table 1). Kondo et al explored the importance of IL-1 β in the elicitation phase.⁵¹ They used a BALB/c mouse model, where the

abdominal skin of mice was shaved and sensitized with 0.5% DNFB. Five days later the ears were challenged with 0.2% DNFB. In addition, they injected varying doses of IL-1Ra, i.d., in the ears at various time points before and after challenge. Mice injected with IL-1Ra right before challenge with doses ranging from 10 to 100 μ g IL-1Ra successfully suppressed the ear swelling at time points 24, 48, and 72 hours after challenge. Furthermore, a time-course study was performed and showed that the suppressive effect of IL-1Ra was time-dependent. Injection of 10 μ g IL-1Ra from 24 hours until zero hours before challenge showed decreased ear swelling, but IL-1Ra injected 1 hour or after DNFB application had no suppressive effects. Petersen et al investigated the role of administering IL-1Ra, i.p., twice daily starting at 16 hours before challenge in filaggrin-deficient flaky tail mice sensitized with nickel. They found reduced ear swelling and a reduction in the total number of IFN γ -producing CD4 and CD8 T cells and IL-17A-producing CD4 T cells (Figure 4).⁸³ Finally, Vennegaard et al treated mice twice daily with IL-1Ra, i.p., both during sensitization and challenge with nickel. In accordance with the previous studies, they found reduced ear swelling in the IL-1Ra-treated mice challenged with nickel.⁵

The ability to inhibit the elicitation phase in mice by blocking the IL-1 β pathway may have clinical relevance as a novel treatment option in patients with ACD; however, no human studies have been conducted to date.

6 | CONCLUSION

IL-1 β undoubtedly plays a major role in the different phases of ACD. Keratinocytes and LCs are the main producers of IL-1 β in the skin. The ITAM-SYK-CARD9 and IL-1R1-MYD88 signaling axis, and the NLRP3 inflammasome are important components in the IL-1 β -driven pathogenesis of ACD. IL-1 β induces T_H1 and T_H17 differentiation and stimulates cytokine production in $\gamma\delta$ T cells and epidermal tissue resident CD8⁺ T cells that subsequently may increase IL-1 β production via a positive feedback loop. Many studies have investigated the function of IL-1 β in ACD mouse models with different contact allergens, treatment options, knock-out genes, and immune cell transplants, but few human studies and especially clinical trials have been conducted. Novel treatment options targeting downstream or upstream IL-1 β signaling pathways have shown promising results in mouse models, and clinical trials are highly relevant to determine the potential of IL-1 β -targeted treatment for ACD.

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AUTHOR CONTRIBUTIONS

Kelvin Yeung: Conceptualization; visualization; writing-original draft; writing-review & editing. **Veronika Mraz:** visualization; writing-review &

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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