



# The role of interleukin-1 in allergy-related disorders

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## Purpose of review

Interleukin-1 $\beta$  (IL-1 $\beta$ ) is a potent proinflammatory cytokine, which is involved in many inflammatory conditions including autoinflammatory and allergic disorders. This review provides insights into recent advances of our understanding of the pathogenesis of IL-1 $\beta$ -associated allergy-related disorders.

## Recent findings

In autoinflammatory as well as allergic diseases such as contact hypersensitivity, atopic dermatitis and bronchial asthma, dysfunctional inflammasome processing has been demonstrated to account for IL-1 $\beta$ -induced inflammation. IL-1-neutralizing drugs have been shown to completely suppress or markedly reduce inflammatory responses in clinical studies and experimental models of urticarial autoinflammatory diseases as well as common allergic disorders.

## Summary

The recent findings support a crucial role for IL-1 $\beta$  and inflammasome components in a variety of allergy-related disorders.

## Keywords

allergy, inflammasome, interleukin-1, urticaria

## INTRODUCTION

Interleukin-1 (IL-1) is a potent inflammatory cytokine that was discovered in the 1970s and was first described as lymphocyte-activating factor [1,2] or leukocytic pyrogen [3]. It belongs to the IL-1 family of ligands which consists of at least 11 members [4]. All of them play a central role in innate immune response. IL-1 $\alpha$  and IL-1 $\beta$  both mediate their biologic responses via activation of the IL-1 receptor type I, whereas IL-1Ra functions as receptor antagonist. Further important representatives of this family are IL-18 and IL-33. Most of the biologic effects in humans including fever, myalgias and joint pain, fatigue and headaches, neutrophilia and increase in acute phase reactants were identified in bone marrow transplanted patients who were injected with either IL-1 $\alpha$  or IL-1 $\beta$  to stimulate haematopoiesis [5–7].

IL-1 $\beta$  is the best-studied cytokine of the IL-1 family. It maintains a central function in defending the organism against infections with pathogenic microorganisms including bacteria [8], fungi [9] and viruses [10]. Also, IL-1 $\beta$  effects are triggered by a variety of host-derived or environmental cellular stressors such as urate crystals, asbestos and skin irritants [11]. Apart from its physiologic role in host protection, IL-1 $\beta$  is known to be important in a

number of severe inflammatory diseases including the rare cryopyrin-associated periodic syndromes (CAPS) and other hereditary and polygenic autoinflammatory diseases. Most of these diseases can be completely controlled by anti-IL-1 $\beta$  treatment [12–15]. In addition, an essential function for IL-1 $\beta$  has been demonstrated in common diseases such as gout [16], type II diabetes [17] and cancer [18].

In the IL-1 $\beta$ -mediated autoinflammatory diseases CAPS and Schnitzler syndrome (SchS), urticarial rash is a hallmark symptom. At the same time, urticarial rashes are among the most frequent symptoms presented to allergists in clinics. Recent findings suggest that IL-1 $\beta$  does not only induce urticarial rashes in autoinflammatory diseases [19] but also plays a role in other allergy-related diseases

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## KEY POINTS

- IL-1 is a key inflammatory cytokine of innate immunity.
- The inflammasome is a cytosolic multiprotein complex that detects pathogens and danger signals and induces the activation of the proinflammatory cytokines IL-1 $\beta$  and IL-18.
- Dysfunctional inflammasome signalling can be observed in a variety of inflammatory conditions including autoinflammatory disorders but also common allergic diseases.
- Anti-IL-1 blockade is effective in depressing the clinical signs and symptoms of a variety of inflammatory disorders.

such as bronchial asthma [20], contact hypersensitivity and atopic dermatitis [21,22<sup>\*\*\*</sup>].

This review will discuss the recent findings in IL-1 $\beta$ -driven pathophysiology with a focus on allergy-related disorders including urticarial auto-inflammatory syndromes, as well as common allergic skin and lung diseases in which IL-1 $\beta$  has been shown to be significantly involved.

## INTERLEUKIN-1 $\beta$ BIOLOGY

IL-1 $\beta$  can mediate inflammatory responses by supporting T-cell survival, upregulation of the IL-2 receptor on lymphocytes, enhancing antibody production of B cells and by promoting B-cell proliferation and T-helper 17 cell differentiation [23]. The main sources of IL-1 $\beta$  are blood monocytes, tissue macrophages and dendritic cells and, to a lesser extent, B lymphocytes and natural killer cells [4]. Secretion of IL-1 $\beta$  from these cells requires a two-step activation process: nuclear factor kappa B-mediated transcriptional upregulation of pro-IL-1 $\beta$ , via Toll-like receptors, for example [24] and caspase-1-driven conversion of pro-IL-1 $\beta$  into its active form. Caspase-1 activity is controlled by a cytosolic multiprotein complex or activation scaffold, also known as the inflammasome [25] (Fig. 1). The inflammasome consists of a nucleotide-binding domain like receptor (NLR), one or more adaptor proteins and caspase-1. Several NLRs have been identified so far; the best-characterized one is the NLR protein 3 (NLRP3). Activation of the NLRP3 inflammasome occurs via recognition of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). So far, a great number of PAMPs and DAMPs have been shown to activate the NLRP3 inflammasome. Amongst others, NLRP3-activating PAMPs can be viral RNA and DNA,

hyphae and bacterial toxins [9,10,26,27]. DAMPs include extracellular ATP, nanoparticles, skin irritants and urate crystals [21,28–30]. PAMP-associated and DAMP-associated NLRP3 activation is followed by the recruitment of apoptosis speck protein (ASC) and procaspase-1 to compose the multiprotein complex that finally leads to cleavage of procaspase-1 into caspase-1. Caspase-1 then mediates the conversion of pro-IL-1 $\beta$  and pro-IL-18 into its active forms. Taken together, the inflammasome detects pathogens and danger signals. This results in the secretion of proinflammatory cytokines which, in turn, attract inflammatory cells to deal with the infection or stressor.

Although the inflammasome reaction in healthy individuals is dependent on PAMPs and DAMPs, there is spontaneous and inappropriate IL-1 $\beta$  secretion in patients with gain of function mutations in the NLRP3 gene as observed in CAPS [31]. Also, mutations in other genes that regulate IL-1 $\beta$  functioning via external inflammasome activation as in Familial Mediterranean fever and hyperimmunoglobulin D (IgD) syndrome [32,33] or via increased IL-1 receptor signalling as in the deficiency in IL-1Ra [34] lead to IL-1 $\beta$ -mediated inflammatory phenotypes.

## AUTOINFLAMMATORY DISORDERS: A PROMINENT ROLE FOR INTERLEUKIN-1 $\beta$

Autoinflammatory diseases are clinical disorders characterized by abnormally increased inflammation which is mediated predominantly by the cells and molecules of the innate immune system [35]. The concept of autoinflammation as opposed to autoimmunity was first proposed in 1999 following the discovery of a mutation in the Tumor necrosis factor (TNF) receptor 1 gene resulting in the TNF receptor-associated periodic syndrome [36]. Autoantibodies and antigen-specific T cells – typical features of autoimmune disorders – are absent in autoinflammatory diseases. Dinarello [37] recently proposed that the term ‘auto’ in autoinflammation may be used as equivalent for IL-1 $\beta$ , as both monogenic and polygenic autoinflammatory diseases demonstrate a dramatic clinical and laboratory response to anti-IL-1-targeted drugs. The increasing understanding of the molecular mechanisms in innate immune responses revealed not only further mutations in genes associated with IL-1 $\beta$  functioning but also exhibited autoinflammatory characteristics in common disorders such as gout, diabetes mellitus and atherosclerosis (Table 1). It should be noted, however, that several disorders including Crohn’s disease and Behçet’s disease are associated with innate and adaptive immune responses

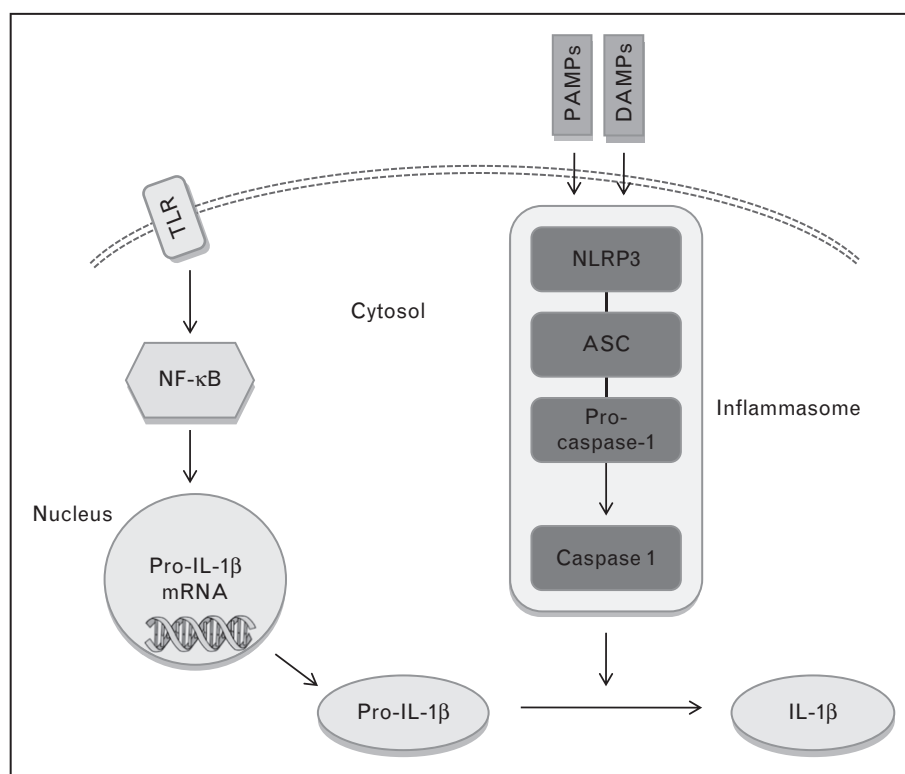


**FIGURE 1.** The nucleotide-binding domain like receptor protein 3 inflammasome. First, cell activation via pattern recognition receptors such as Toll-like receptors (TLRs) leads to nuclear factor kappa B (NF-κB) – induced upregulation of pro-IL-1β expression. Second, specific pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) can activate nucleotide-binding domain like receptor protein 3 (NLRP3) which results via recruitment of apoptosis speck protein (ASC) and procaspase-1 in assembly of the inflammasome. Procaspase-1 is cleaved into active caspase-1, which in turn promotes the processing of pro-IL-1β into the biologically active IL-1β.

displaying both autoinflammatory and autoimmune mechanisms at the same time [38].

### INTERLEUKIN-1β-DRIVEN DISEASES PRESENTING WITH URTICARIAL RASH

Urticarial rash, that is, pruritic wheal and flare type skin reactions, can be seen in a variety of clinical disorders. These include acute and chronic spontaneous urticaria, inducible urticarias, as well as type-I allergic reactions to drugs or food. Urticarial rash is also present in systemic inflammatory diseases like urticarial vasculitis and autoinflammatory disorders. Within the autoinflammatory disorders, CAPS and SchS are regularly associated with urticarial rash.

#### Cryopyrin-associated periodic syndromes

CAPS are the prototypes of hereditary periodic fever syndromes with a gain-of-function mutation in the NLRP3 gene. They are characterized by an

inflammatory phenotype due to excessive IL-1β activation. Interestingly, the main source of NLRP3-mediated IL-1β secretion in the skin of CAPS patients has been identified to be mast cells [19], the key effector cells in urticaria and allergic skin reactions [39]. Clinical features in CAPS include chronic urticarial rash and a variety of systemic symptoms such as recurrent fever, malaise, joint and ocular involvement, headaches and severe neurologic manifestations. CAPS consist of three subtypes with different severity. Familial cold-associated syndrome is the mildest form and is characterized by mainly cold-induced symptoms, followed by the Muckle–Wells syndrome with an intermediate phenotype, continuous symptoms and flares. Neonatal-onset multisystem inflammatory disease presents the most severe subtype with destructive arthritis and central nervous system involvement.

A very good and rapid treatment response has recently been demonstrated in clinical trials with IL-1 neutralizing drugs in all subtypes of CAPS [12,40,41]. Apart from sustained remission of symptoms [42\*],

**Table 1. Classification of autoinflammatory diseases**

| Disease                                           | Gene           | Proposed mechanism                                                          | Phenotype                    |
|---------------------------------------------------|----------------|-----------------------------------------------------------------------------|------------------------------|
| Monogenic diseases                                |                |                                                                             |                              |
| Hereditary periodic fever syndromes               |                |                                                                             |                              |
| FMF                                               | MEFV           | Inflammasome activation                                                     | Erysipelas-like skin lesions |
|                                                   |                |                                                                             | Fever                        |
|                                                   |                |                                                                             | Arthralgia                   |
| TRAPS                                             | TNFRSF1A       | Protein misfolding                                                          | Abdominal pain               |
|                                                   |                |                                                                             | Migratory erythema           |
|                                                   |                |                                                                             | Fever                        |
| HIDS                                              | MVK            | Inflammasome activation                                                     | Myalgia                      |
|                                                   |                |                                                                             | Arthralgia                   |
|                                                   |                |                                                                             | Abdominal pain               |
| CAPS                                              | NLRP3          | Intrinsic inflammasomopathy                                                 | Morbilliform rash            |
|                                                   |                |                                                                             | Aphthae                      |
|                                                   |                |                                                                             | Fever                        |
| Other monogenic diseases                          | PSTPIP1/CD2BP1 | Abnormal PSTPIP1 binding to pyrin causing increased IL-1 $\beta$ activation | Arthralgia                   |
|                                                   |                |                                                                             | Abdominal pain               |
|                                                   |                |                                                                             | Urticarial rash              |
| PAPA syndrome                                     | PSTPIP1/CD2BP1 | Abnormal PSTPIP1 binding to pyrin causing increased IL-1 $\beta$ activation | Pyoderma gangrenosum         |
| Blau syndrome                                     | NOD2/CARD15    | NF- $\kappa$ B activation disorder                                          | Fever                        |
|                                                   |                |                                                                             | Arthralgia                   |
|                                                   |                |                                                                             | CNS symptoms                 |
| DIRA                                              | IL1RN          | Absence of negative IL-1 $\alpha$ or IL-1 $\beta$ regulator                 | Pyoderma gangrenosum         |
|                                                   |                |                                                                             | Acne                         |
|                                                   |                |                                                                             | Arthritis                    |
| NLRP12-associated cold autoinflammatory syndrome  | NLRP12         | NF- $\kappa$ B activation disorder                                          | Arthritis                    |
|                                                   |                |                                                                             | Sarcoidal papules            |
|                                                   |                |                                                                             | Uveitis                      |
| Majeed syndrome                                   | LPIN2          | Unknown                                                                     | Arthritis                    |
|                                                   |                |                                                                             | Painful papules              |
|                                                   |                |                                                                             | Bone pain                    |
| Polygenic diseases                                | complex        | Unknown                                                                     | Exostosis                    |
|                                                   |                |                                                                             | Urticarial rash              |
|                                                   |                |                                                                             | Arthralgia                   |
| Diseases with proposed autoinflammatory mechanism |                |                                                                             | Arthritis                    |
|                                                   |                |                                                                             | Maculopapular rash           |
|                                                   |                |                                                                             | Fever                        |
| Schnitzler syndrome                               |                | Inflammasome activation                                                     | Arthritis                    |
|                                                   |                |                                                                             | Maculopapular rash           |
|                                                   |                |                                                                             | Fever                        |

**Table 1 (Continued)**

| Disease                                              | Gene    | Proposed mechanism                            | Phenotype                 |
|------------------------------------------------------|---------|-----------------------------------------------|---------------------------|
|                                                      |         |                                               | Fever                     |
|                                                      |         |                                               | Arthralgia                |
|                                                      |         |                                               | Bone pain                 |
| <b>Probable autoinflammatory diseases</b>            |         |                                               |                           |
| Crohn's disease                                      | complex | NF- $\kappa$ B activation disorder            | Gastrointestinal symptoms |
| Behçet's disease                                     |         | Unknown                                       | Bipolar aphthae           |
| Sweet syndrome                                       |         | Unknown                                       | Painful papules           |
|                                                      |         |                                               | Fever                     |
| CRMO                                                 |         | Unknown                                       | Bone pain                 |
|                                                      |         |                                               | Fever                     |
| SAPHO syndrome                                       |         | Unknown                                       | Pustulosis, acne          |
|                                                      |         |                                               | Bone pain                 |
| <b>Common diseases with autoinflammatory aspects</b> |         |                                               |                           |
| Gout                                                 | complex | Crystal-induced inflammasome activation       | Arthritis                 |
|                                                      |         |                                               | Fever                     |
| Type II diabetes                                     |         | Hyperglycemia-induced inflammasome activation | Hyperglycemia             |
| Atherosclerosis                                      |         | Unknown                                       | Cardiovascular disease    |

AOSD, adult-onset Still's disease; CAPS, cryopyrin-associated periodic syndromes; CRMO, chronic recurrent multifocal osteomyelitis; DIRA, deficiency in IL-1R $\alpha$ ; FMF, Familial Mediterranean fever; HIDS, hyper-IgD syndrome; IL-1, interleukin 1; NF- $\kappa$ B, nuclear factor kappa B; NLRP3, nucleotide-binding domain like receptor protein 3; PAPA, pyogenic arthritis with pyoderma gangrenosum and acne; SAPHO, synovitis acne pustulosis hyperostosis osteitis; sJIA, systemic-onset juvenile idiopathic arthritis; TRAPS, TNF receptor-associated periodic syndrome.

anti-IL-1 blockade also showed significant improvement in health-related quality of life [43].

### Schnitzler syndrome

Urticarial rash is also a key symptom in SchS, a late-onset autoinflammatory disease. SchS usually starts around the age of 50 and is characterized by recurrent urticarial rash associated with a monoclonal gammopathy (IgM or rarely IgG class). Further symptoms are episodes of fever, myalgias, bone and joint pain as well as lymphadenopathy. The pathogenesis of SchS and the relevance of the gammopathy have still to be unravelled. A recent study [44] with peripheral blood mononuclear cells from SchS patients showed a marked increase in IL-1 $\beta$  secretion, as compared with healthy controls. Also, the inflammasome component ASC was found to be significantly downregulated, whereas the ATP receptor P2X<sub>7</sub>, which is implicated in inflammasome induction, was upregulated compared with healthy controls. It was therefore suggested that SchS represents an intrinsic inflammasomopathy similar to that seen in CAPS patients. Very recently, an upregulation of IL-1 $\beta$  has also been found in lesional skin of SchS patients [45].

Antihistamines, NSAIDs or immunosuppressives show no or only very limited efficacy in the treatment of SchS further indicating that histamine or the adaptive immune system are not critically involved in the pathogenesis of the disease. In contrast, the use of anti-IL-1 blockers in single cases and first clinical studies [46,47] has revealed highly beneficial effects of IL-1-neutralizing drugs as comparable to those seen in CAPS.

### A FURTHER ROLE FOR INTERLEUKIN-1 IN ALLERGY

Allergies are abnormal reactions of the body to a previously encountered allergen introduced by inhalation, injection, ingestion or skin contact. Allergens are usually harmless substances which are erroneously recognized as harmful pathogens by the host. The main effector mechanisms in allergy are T-cell-mediated inflammation (for example in contact hypersensitivity) and IgE-triggered release of histamine from mast cells (for example in type I reactions). Recent findings suggest that inflammasome-dependent IL-1 $\beta$  activation also plays a role in different allergic disorders.

### Contact hypersensitivity

Contact hypersensitivity is characterized by T-cell-driven skin inflammation elicited in response to various haptens, for example chemicals or metallic ions such as nickel. Skin irritants can induce the activation of the proinflammatory cytokine IL-1 $\beta$  which can then participate in Langerhans cell migration and lymphocyte recruitment, thus, promoting skin inflammation [48]. How skin irritants activate IL-1 $\beta$  was unknown until recently. Watanabe *et al.* [21] were able to show that the inflammasome is involved in these processes and contributes to contact hypersensitivity. They showed that trinitrochlorobenzene (TNCB), a potent hapten, can induce caspase-1-dependent IL-1 $\beta$  activation from human keratinocytes. Also, TNCB-induced contact dermatitis was found to be reduced in ASC and NLRP3 knockout mice. Inflammasome involvement in the development of contact hypersensitivity is further underlined by another study [49] showing resistance to contact hypersensitivity in mice lacking the ATP receptor P2X<sub>7</sub> which is implicated in inflammasome activation. Furthermore, signalling via the IL-1 receptor has been demonstrated to be necessary both in the sensitization period and elicitation of contact hypersensitivity [50<sup>\*</sup>]. In line with these results, the use of anti-IL-1 antagonists suppresses the clinical symptoms of contact hypersensitivity in mice [51].

### Atopic dermatitis

Atopic dermatitis is a Th2-mediated chronic inflammatory skin disorder in which T-cell responses to environmental or food allergens are associated with the development and aggravation of the disease. It is known that keratinocytes contain the NLRP3 inflammasome and that ultraviolet B irradiation leads to enhanced IL-1 $\beta$  secretion [52]. Recently, it was shown that house dust mite allergens act as danger signals in the skin and can also induce inflammasome-dependent IL-1 $\beta$  secretion from keratinocytes [22<sup>\*\*</sup>].

In addition to allergens, pathogens such as *Staphylococcus aureus* or herpes simplex virus are correlated with disease exacerbation in atopic dermatitis. Colonization with *S. aureus* is frequently found in atopic dermatitis and is thought to be related to a defective innate immune system [53]. In this regard, it is also noteworthy that haemolysins and bacterial lipoproteins from *S. aureus* are potent PAMPs that can activate the NLRP3 inflammasome [54].

It may, therefore, be assumed that allergen-induced and pathogen-induced inflammasome

activation can account for disease exacerbation in atopic dermatitis patients.

### Bronchial asthma

Asthma is characterized by chronic airway inflammation and hyperresponsiveness to external stimuli. Different experiments in mice have indicated an important role for IL-1 in Th2-related cytokine production and airway hyperresponsiveness [55,56]. Recently, the Th2 response has been linked to the activation of the NLRP3 inflammasome in a murine ovalbumin-induced asthma model. Besnard *et al.* [57<sup>\*\*</sup>] showed a decrease in IL-1 $\beta$ -mediated dendritic cell recruitment, Th2 lymphocyte activation and reduced proinflammatory cytokines in NLRP3 knockout mice. In another study [58], NLRP3 single nucleotide polymorphisms were found to be associated with a higher susceptibility to aspirin-induced asthma and food-induced anaphylaxis. Finally, there is also evidence from several animal asthma models that treatment with IL-1-neutralizing drugs results in a reduced airway hyperreactivity, less inflammatory infiltration and a decrease in Th2 cytokines [59–62].

### CONCLUSION

IL-1 has been known for many years to be a potent proinflammatory cytokine. The concept of autoinflammation and the discovery of the molecular basis of autoinflammatory diseases have revealed a much better understanding of IL-1 $\beta$  activation and processing. In contrast to former presumptions of non-specific responses, it could be demonstrated that the innate immune system acts via specific pathways in which IL-1 $\beta$  exerts a major role. Recent work showed that inflammasome dysfunction is not limited to rare hereditary periodic fever syndromes. It also occurs in common allergic disorders such as contact hypersensitivity, which is primarily mediated by adaptive immune responses. This exemplifies how innate and adaptive immune responses are closely linked to each other. Recognition of the prominent role of IL-1 $\beta$  in many inflammatory conditions also led to successful use of anti-IL-1-blocking agents. For the future, inflammasome components represent interesting targets to be investigated for the development of new specific drugs in allergy-related and other inflammatory disorders.

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### Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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