

Role of Interleukin 1 in Atopic Dermatitis

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KEYWORDS

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• Neutrophils • Cytokines

KEY POINTS

- Interleukin 1 (IL-1) ligands
- Signal transduction patterns of IL-1 receptors
- Inflammasome-mediated inflammation
- IL-1 activation by inflammasome
- Naturally occurring antagonists
- IL-1/IL-1 receptor antagonist balance
- Role of IL-1 in atopic dermatitis

OVERVIEW OF INTERLEUKIN 1

Interleukin-1 (IL-1) is a potent inflammatory cytokine that plays a central role in the innate immune response.¹ Discovered in the 1970s, it was initially named lymphocyte-activating factor, catabolin, and endogenous pyrogen because of its proinflammatory effects.² IL-1 mediates the acute phase of inflammation by inducing local and systemic responses, such as pain sensitivity, fever, vasodilation, and hypotension. It also promotes the expression of adhesion molecules on endothelial cells, which allows the infiltration of inflammatory and immunocompetent cells into the tissues.³

IL-1 is secreted mainly by monocytes, tissue macrophages, and dendritic cells, but is also expressed by B lymphocytes, natural killer (NK) cells, and epithelial cells.⁴ In the epidermis, IL-1 is

produced by keratinocytes under the stimulation of proinflammatory cytokines, with the stratum corneum serving as a major reservoir of active IL-1. The release of IL-1 from the epidermis after activation is a primary event that promotes inflammatory skin conditions through the induction of various cytokines, proinflammatory mediators, and adhesion molecules.^{5,6}

IL-1: An Extensive Family of Ligands

IL-1 belongs to a family of ligands and receptors.⁷ The classic members IL-1 α and IL-1 β mediate their biological responses via activation of the IL-1 receptor type I, which is expressed by almost all cell types. The IL-1 receptor antagonist (IL-1Ra), the third member of the IL-1 family, has antiinflammatory activity because of its ability to bind to IL-1

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receptor type I, thus preventing the binding of the proinflammatory molecules IL-1 α and IL-1 β .⁴

With the ongoing discovery of the mechanisms and pathways of inflammation, receptor response, and cytokine expression, the IL-1 family has expanded to the current 11 members shown in **Table 1**. The IL-1R family has also expanded to 9 distinct genes and includes coreceptors, decoy receptors, binding proteins, and inhibitory receptors.⁸

For some investigators, the properties of IL-1 still remain the model for mediating inflammation, describing IL-1 as capable of initiating its action by binding to the ligand-binding chain (IL-1RI), following a series of events that includes recruitment of the coreceptor chain (accessory protein or IL-1RAcP). As a consequence, a complex is formed of IL-1RI plus IL-1 plus the coreceptor, initiating the signal by recruitment of the adaptor protein MyD88 to the Toll-IL-1 receptor (TIR) domain. This concept established the share of functions by different cytokines that attach to the same type of receptors, which is followed by the phosphorylation of several kinases, the nuclear factor (NF) kappa light chain enhancer of activated B cells (NF- κ B) translocates to the nucleus, and the expression of a large range of inflammatory genes takes place.

Signal transduction in IL-1-stimulated cells has been reviewed in detail by Weber and colleagues⁹ with similar statements and conclusions. IL-33, a cytokine with high level of involvement in atopic dermatitis (AD) immunopathogenesis, has been included in the IL-1 family of ligands. IL-33 binds to ST2, a member of the TIR superfamily that does not activate NF- κ B and has been suggested as an important effector molecule of T-helper type 2

(Th2) cell responses; it also recruits the IL-1RAcP. T-helper type 2 (Th2)-like properties characterize IL-33. The 6 proinflammatory members of the IL-1 family each recruit the IL-1RAcP coreceptor with the TIR domain and MyD88 docks to each, making their pathogenic action a common mechanism. IL-1Ra, IL-1 α , and IL-1 β have a similar affinity to IL-1RI. The IL-1 ligands, their coreceptors, and main properties are presented in **Table 1**.^{1,10,11}

From this perspective, the expression of IL-1 receptor stimulation has complex implications: ligands mediate their biological responses via activation of specific receptors and share the target for the immunoglobuline (Ig)-like receptor binder, where all ligands can stimulate the IL-1 receptor. This characteristic is unique for the IL-1 family of receptors because of the presence of the TIR domain in the cytoplasmic segment of each member in this class.

Particular attention should be given to IL-37 and IL-33, because of their capacity to interact with the IL-1 receptor and to translocate directly to the nucleus. These unique ligands of the IL-1 family, on interaction with the IL-1 receptor, function as proinflammatory (IL-33) and as antiinflammatory (IL-37) cytokines, which is a special property of the ligands, working as a guarantee of the inflammatory response; for example, expression of the N-terminal amino acids of IL-1 α stimulates IL-8 production in the presence of complete blockade of the IL-1RI on the cell surface. Because of this property, the ligands mentioned earlier were named by Dinarello and colleagues⁸ as dual-function cytokines.

With the exception of IL-1Ra, each member of the IL-1 family is first synthesized as a precursor without a clear signal peptide for processing and

Table 1 The IL-1 receptor family of ligands			
Name	Receptor	Coreceptor	Property
IL-1 α	IL-1R1	IL-1RAcP	Proinflammatory
IL-1 β	IL-1R1	IL-1RAcP	Proinflammatory
IL-1Ra	IL-1R1	NA	Antagonist IL-1 α and β
IL-18	IL-18R α	IL-18R β	Proinflammatory
IL-36Ra	IL-1Rp2	NA	Antagonist IL-36 α , β , γ
IL-36 α	IL-1Rp2	IL-1RAcP	Proinflammatory
IL-37	IL-18R α	Unknown	Antiinflammatory
IL-36 β	IL-1Rp2	IL-1RAcP	Proinflammatory
IKL-36 γ	IL-1Rp2	Unknown	Proinflammatory
IL-38	Unknown	IL-1RAcP	Unknown
IL-33	ST2	IL-1RAcP	Th2 Response, Proinflammatory

Abbreviations: IL-1RI, type 1 interleukin 1 ligand-binding chain; IL-1RAcP, interleukin 1 receptor accessory protein coreceptor chain; IL-1Rp, interleukin 1 receptor protein; IL-1Ra, interleukin 1 receptor antagonist.

secretion, and none are found in the Golgi apparatus. IL-1 α and IL-33 are similar in that their precursor forms can bind to their respective receptor and trigger signal transduction; both have a dual function: in addition to binding to their respective cell surface receptors, the intracellular precursor forms translocate to the nucleus and influence transcription, and their nuclear function is transcription of proinflammatory genes. IL-37 is a unique ligand in the IL-1 family because it functions as an antiinflammatory cytokine; activation of this cytokine generates a net decrease in inflammation.^{11–14} **Fig. 1** shows a summary of IL-1 receptor signaling and includes all activation details for each member of the IL-1 receptor family, as proposed by Dinarello and colleagues⁸ in 2009 with some additions based on the latest discoveries.⁷

Characterization of IL-1

IL-1 α is a unique member of the cytokine family synthesized as a precursor protein Pro-IL-1 α , with the mature form resulting from the removal of N-terminal amino acids. Both Pro-IL-1 α and mature IL-1 α are biologically active.⁸ IL-1 α expression can promote local inflammation by functioning both as secreted and membrane-bound proteins.¹⁵

Other publications assign proinflammatory properties of IL-1 α in connection to the development of atherosclerotic vascular disease.¹⁶

IL-1 β is the best-studied cytokine of the IL-1 family; it plays a central role in defensive mechanisms against pathogens. However, its expression can be triggered by a variety of host-derived or environmental cellular stressors, including skin

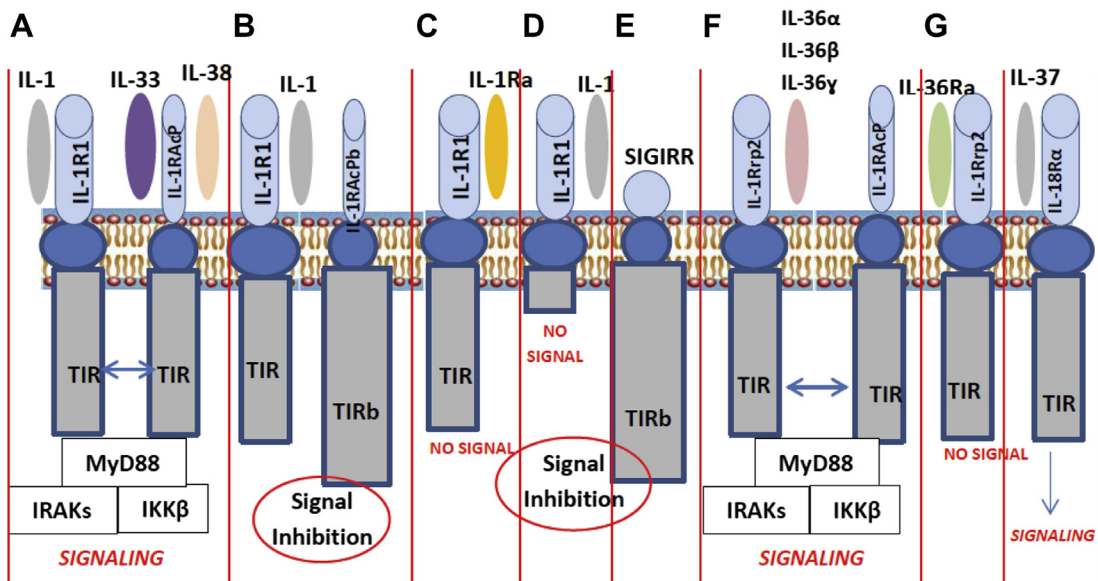


Fig. 1. Signaling patterns for the IL-1 ligands. (A) IL-1/IL-1RI/IL-1RAcP/IL-33 binding. Formation of the receptor heterodimeric complex. The TIR domain of each receptor chain recruits MyD88, followed by phosphorylation of IL-1R-associated kinases (IRAKs) and inhibitor of NF κ B kinase (IKK), resulting in a signal to the nucleus. (B) Formation of the hemodimeric complex (brain and spinal cord) between the variant IL-1RAcPb and IL-1 or IL-1 and IL-1RI. This complex fails to recruit MyD88, and there is inhibition of the IL-1 signal. The failure to recruit MyD88 may be because of an altered TIR domain (TIRb). (C) IL-1Ra binds to IL-1RI, but there is no signal because there is failure to form a complex with IL-1RAcP. (D) IL-1 binds to the IL-1RII but, lacking a cytoplasmic segment, there is no signal. (E) Because of an altered TIR domain (indicated as TIRb), SIGIRR inhibits IL-1 and TLR signaling. SIGIRR can form a complex with IL-33 (not shown) and inhibit IL-33 signaling. (F) IL-1Rrp2 binds IL-36, IL-36, or IL-36 and forms a complex with IL-1RAcP. The TIR domain of each receptor chain approximates and recruits MyD88. (G) IL-36Ra binds to IL-1Rrp2 but fails to form a complex with IL-1RAcP. Thus, IL-36Ra prevents the binding of IL-36, IL-36, or IL-36 to IL-1Rrp2, and IL-36Ra is the natural receptor antagonist IL-36. IKK, inhibitor of NF κ B kinase; IL-1Ra, interleukin 1 receptor antagonist; IL-1RAcP, interleukin 1 receptor accessory protein coreceptor chain; IL-1RI, type 1 interleukin 1 ligand-binding chain; IL-1Rp, interleukin 1 receptor protein; MyD88, intracellular adaptor protein; SIGIRR, single IL-1-related receptor; TIR, Toll-IL-1 receptor domain; TIRb, altered TIR domain; TLR, Toll-like receptors. (Data from Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood* 2011;117(14):3720–32; and Dinarello CA. Immunologic and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009;27:519–50.)

irritants. It had been mentioned as mediator of inflammatory responses by supporting T-cell survival, upregulating the IL-2 receptor on lymphocytes, enhancing antibody production of B cells, and promoting B-cell proliferation and T-helper 17 cell differentiation. Recent studies have suggested that IL-1 β does not only induce urticarial rashes in autoinflammatory diseases but is also important in the expression of other allergy-related diseases such as bronchial asthma, contact hypersensitivity, and AD.¹

IL-1 and Inflammasome-mediated Inflammation

The expression of IL-1 β from cells requires NF- κ B-mediated transcriptional upregulation of pro-IL-1 β and caspase-1-driven conversion of pro-IL-1 β into its active form. Caspase-1 activity is controlled by a cytosolic multiprotein complex or activation scaffold, also known as the inflammasome.¹

The complex detects pathogens and danger signals and induces the activation of the proinflammatory cytokines, which, in turn, attract inflammatory cells to deal with the infection or stressor. In autoinflammatory as well as allergic diseases such as contact hypersensitivity, bronchial asthma, and AD, dysfunctional inflammasome processing has been shown to account for IL-1 β -induced inflammation. It is an IL-1 activating platform; cryopyrin (NLRP3, NLRP1), IPAF, and AIM2, are the key pathways to produce its activation, and have a role as key molecules in regulating

the inflammatory cytokine processing platform. **Fig. 2** shows a model proposed by Goldbach-Mansky¹⁷ of the mechanisms mentioned earlier. Cryopyrin, apoptosis speck protein (ASC), cardinal, and 2 procaspase-1 molecules assemble to form the cryopyrin inflammasome that activates caspase-1. Active caspase-1 enzymatically cleaves inactive IL-1 β into its active form.

The activation mechanisms of the inflammasome have been studied to determine what subfamilies of NOD receptors produce cytokine activation and release on presentation of different activators. At present, there are 4 accepted mechanisms for which the inflammasome is activated: NLRP3 (activated by several mechanisms, including extracellular ATP from the foreign invaders, crystal molecules engulfed by the phagocytes, secreting lysosomes detected by the inflammasome or activated reactive oxygen species [ROS]. The final product is membrane pore formation), NLRP1 (found in experimental murine models, by an undefined mechanism, assuming to have similar pathways than NLRP3), IPAF (activated by gram-negative bacteria with type III or IV secreting substances), and AIM2 (a cytosolic double-stranded DNA sensor that induces caspase-1-dependent IL-1 β maturation).¹⁸

For the nucleotide-binding domain-like receptor protein 3 inflammasome (NLRP3), the most accepted and studied inflammasome, the pathway starts with cell activation via pattern recognition receptors such as Toll-like receptors (TLRs), leading to NF- κ B-induced upregulation of pro-IL-1b

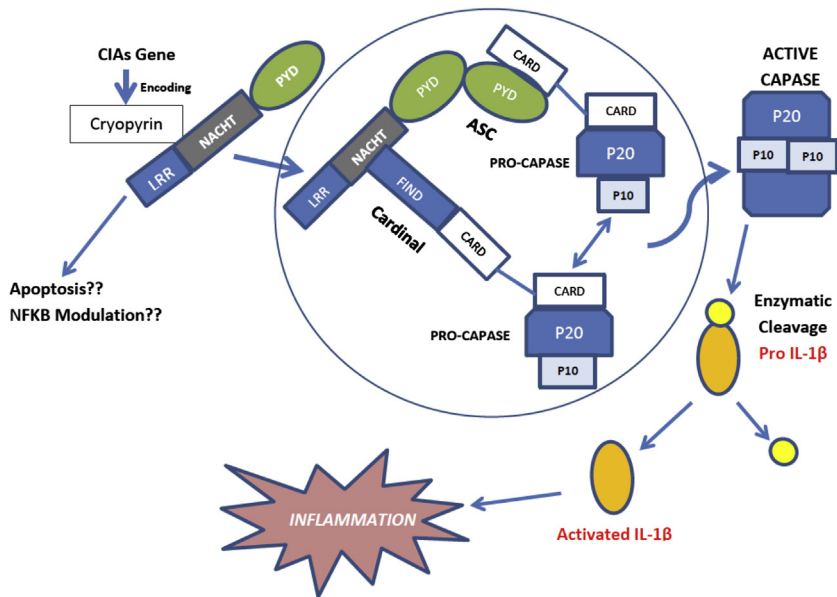


Fig. 2. Mechanism of inflammasome activation of IL-1. (Adapted from Goldbach-Mansky R. Blocking IL-1 in rheumatic diseases. Ann N Y Acad Sci 2009;1182:111–23; with permission.)

expression. Specific pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) can activate NLRP3, which, via recruitment of ASC and procaspase-1, results in assembly of the inflammasome. Procaspase-1 is cleaved into active caspase-1, which in turn promotes the processing of pro-IL-1 β into the biologically active IL-1 β . The major currently accepted models for NLRP3 inflammasome activation are presented in **Fig. 3**. The postulated mechanisms are not exclusive: the NLRP3 agonist, ATP, triggers P2X7-dependent pore formation by the pannexin-1 hemichannel,

allowing extracellular NLRP3 agonists to enter the cytosol and directly engage NLRP3. Crystalline or particulate NLRP3 agonists are engulfed, and their physical characteristics lead to lysosomal rupture. The NLRP3 inflammasome senses lysosomal content in the cytoplasm; for example, via cathepsin-B-dependent processing of a direct NLRP3 ligand. All DAMPs and PAMPs, including ATP and particulate/crystalline activators, trigger the generation of ROS. An ROS-dependent pathway triggers NLRP3 inflammasome complex formation. Caspase-1 clustering induces autoactivation and caspase-1-dependent maturation and

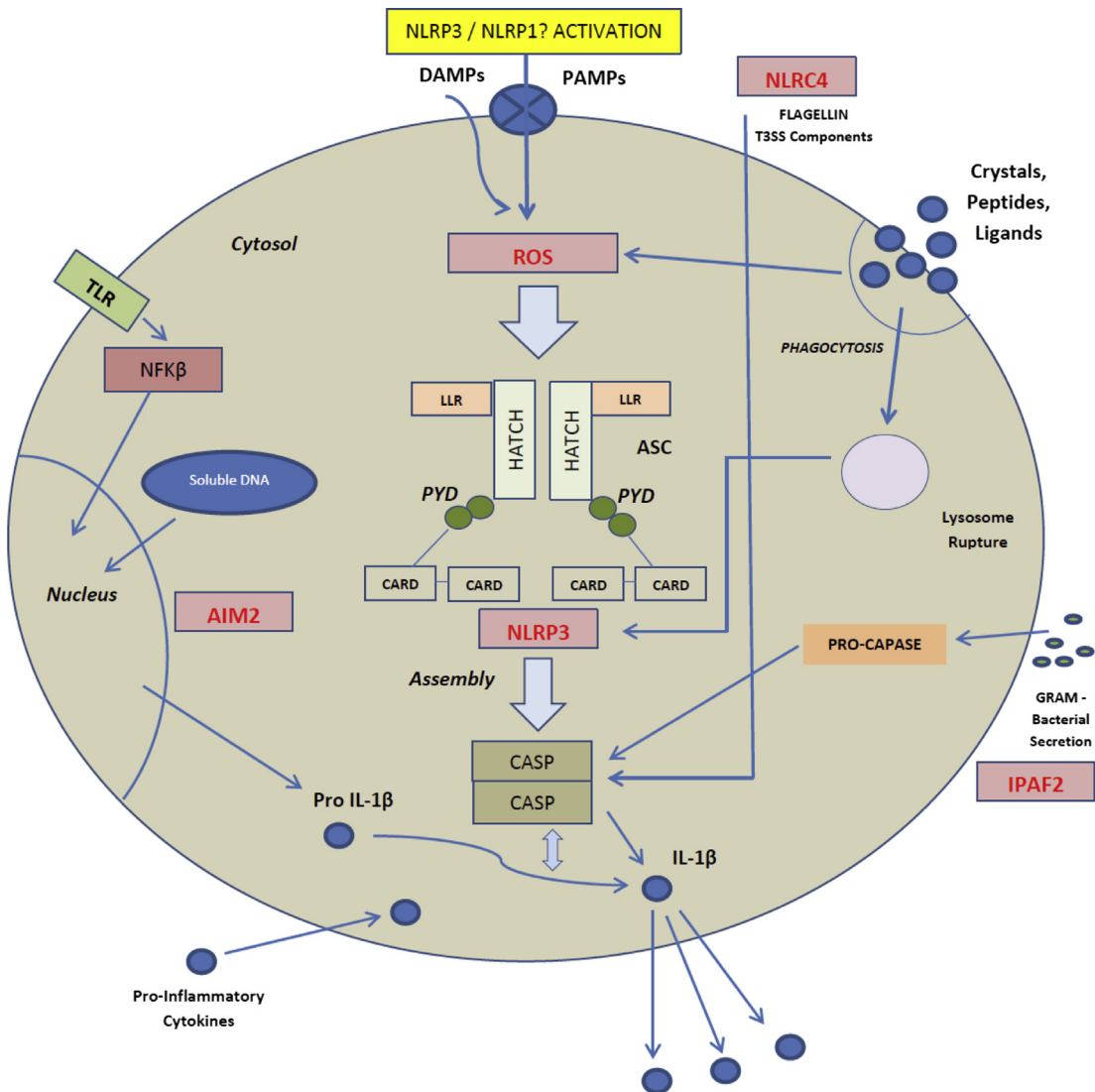


Fig. 3. The major models for inflammasome activation. CARD, N-terminal caspase recruitment; LRR, C-terminal leucine-rich repeats; NACHT, nucleotide-binding area oligomerization domain; NLR, Nodlike receptors; PPR, pattern recognition receptors; PYD, pyrin domains; ROS, reactive oxygen species. (Data from Schroder K, et al. The inflammasomes. *Cell* 2010;140:821–32.)

secretion of proinflammatory cytokines, such as IL-1b and IL-18.

Naturally Occurring Antagonists

IL-1Ra is the only known naturally occurring receptor antagonist. It competitively binds the IL-1 receptor to antagonize IL-1 activity without any agonist function.⁵ There are 2 isoforms of IL-1Ra: a secretory form (sIL-1Ra) and an intracellular form (icIL-1Ra). The sIL-1Ra is mainly secreted by activated monocytes, macrophages, and neutrophils, whereas the icIL-1Ra remains in the cytoplasm of keratinocytes and other epithelial cells, monocytes, and fibroblasts.^{5,19} Endogenous IL-1Ra is expressed in experimental animal models of disease as well as in human autoimmune and chronic inflammatory diseases.²⁰ Neutralization of IL-1Ra has shown the importance of this natural antiinflammatory cytokine in arthritis, colitis, and granulomatous pulmonary disease. Treatment with recombinant human IL-1Ra in patients with rheumatoid arthritis for 6 months showed clinical and radiographic improvements in joint disease; however, the same therapy did not show any benefit in sepsis syndrome.¹⁹

IL-1/IL-1Ra Balance Plays an Important Role in Skin Inflammatory Diseases

The balance between IL-1Ra and IL-1 is important in maintaining the homeostasis in the skin because IL-1Ra inhibits the binding of IL-1 α and IL-1 β to the two types of IL-1 receptors. Studies have reported development of UVB-induced polymorphic light eruptions associated with decreased expression of IL-1Ra, whereas a relative increase in bioavailable IL-1 contributed to psoriasis vulgaris.⁴ The ratio of IL-1Ra to IL-1 α was significantly increased in the stratum corneum of active lesions from patients with psoriasis and AD.⁵ It therefore seems that the increased ratio of IL-1Ra to IL-1 α is a nonspecific phenomenon that can occur in various kinds of cutaneous inflammation. Recent findings also suggest that inflammasome-dependent IL-1 β activation plays a role in other allergic disorders such as contact hypersensitivity and asthma.¹

In AD, T-cell responses to environmental or food allergens are associated with the development and aggravation of the disease. An enhanced endogenous secretion of IL-1 α leading to increased IL-2 activity in blood mononuclear cells following allergen exposure in children with food sensitive AD has been reported.¹⁹ In addition, both ultraviolet B irradiation and house mite allergens have been shown to induce inflammasome-dependent IL-1b secretion from keratinocytes.¹ *Staphylococcus aureus* or herpes simplex virus

infections are also correlated with disease exacerbation in AD. Hemolysis and bacterial lipoproteins from microbes can activate the NLRP3 inflammasome, leading to disease exacerbation in AD.¹

Acute and Chronic Phases of immunoglobulin E and T-cell-mediated AD

In the acute phase of AD, Langerhans cells are activated on binding of allergens by means of specific immunoglobulin (Ig) E and Fc ϵ RI. They produce monocyte chemotactic protein 1 (MCP-1) and IL-16. Allergen-derived peptides are presented to T cells by Langerhans cells that induce a Th2 profile. After migration into the skin, the recruited monocytes differentiate into inflammatory dendritic epidermal cells (IDEC) and produce IL-1, IL-6, and tumor necrosis factor α (TNF- α). Their secretion of IL-12 and IL-18 contributes to the switch from Th2 to Th1/0 that leads to the chronic phase of the disease. In the chronic phase and during exacerbation episodes, allergen-induced and pathogen-induced inflammasome activation become the most characteristic events, with IL-12/18 producing changes from Helper T Lymphocyte type 2 (TH2) to TH1 to initiate and maintain the pathways that characterize the chronification process.

Evidence that supports the role of IL-1 in AD

Tissue-resident cells such as keratinocytes play an important role in directing immune responses. In the presence of activated T cells, epithelial cells seem to be a more significant source of IL-1 β than monocytes. IL-1 secretion and the physical contact between keratinocytes and activated infiltrating T cells may be central to the development of chronic inflammatory skin conditions such as AD.⁶

IL-1 and its ligands are key inflammatory cytokines of innate immunity and play a role in the pathogenesis of AD. There is increasing clinical evidence suggesting that IL-1 has a significant role in the inflammatory pathways involved in the acute and chronic phase of the disease. IL-1 plays a significant role in the skin barrier function, which is disrupted in the acute phase of AD. Changes from TH2 to TH1 expression, instigated by IL-1 ligands (IL-18), are associated with the chronification of the AD lesions. Anti-IL-1 blockade is effective in depressing the clinical signs and symptoms of a variety of inflammatory disorders.

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.¹ In the United States, some IL-1-neutralizing drugs have been approved for use in specific inflammatory diseases, including anakinra (Kineret), a

combinant human IL-1 receptor antagonist that binds to IL-1 receptor type 1 and that was approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis in 2001; rilonacept (Arcalyst), a soluble IL-1 receptor immunoglobulin recombinant human IL-1 receptor-immunoglobulin fusion protein that exerts its mechanism of action by binding to IL-1 α and IL-1 β and was approved by the FDA for the treatment of Cryopyrin-associated periodic syndrome (CAPS) in February 2008; canakinumab (Ilaris), a humanized anti-IL-1 β antibody that binds to IL-1 β and was approved by the FDA for the treatment of CAPS in July 2009. Other treatments include colchicine, TNF blockade, thalidomide, azathioprine, nonsteroidal antiinflammatory drugs, and corticosteroids.¹⁷

Important findings support the role of the inflammasome and IL-1 β in autoinflammatory as well as allergic diseases such as AD. Dysfunctional inflammasome processing has been shown to account for IL-1 β -induced inflammation, supporting the crucial role for IL-1 β and inflammasomes in a variety of allergy-related disorders including AD.¹

Watanabe and colleagues²¹ conducted an in vivo/in vitro study to determine whether the inflammasome contributes to contact hypersensitivity (CS) or to eczema. The results show the involvement of IL-1 β -processing inflammasome CS. The proinflammatory stimulus was caused by NALP3 inflammasome-dependent IL-1 β production in the skin. In CS or in eczema, delayed-type hypersensitivities, the immune response depends on the concomitant activation of the innate and adaptive immune systems, including IL-1 β /IL-18 activation in the skin.

There is an increase of IL-2 activity in mononuclear cells from patients with food-sensitive AD following allergen exposure. Soluble IL-2 receptor (sIL-2R) is an indirect marker of T-cell activation by IL-2; raised concentrations have been described in adults with AD. In vitro studies suggest that IL-2 secretion by TH cells is antigen driven and also dependent on IL-1 expression by cells of the macrophage/monocyte series. Some data suggest that IL-1 upregulates the expression of high-affinity receptors for IL-2 on TH1 cells. In addition, there is an enhanced endogenous secretion of IL-1 α and increased stimulation of IL-2 receptors in children with AD.^{19,22}

Transgenic mice expressing IL-18 from the keratin 5 promoter show many features of AD: acanthosis, a mixed inflammatory cell infiltrate, increased cytokine and chemokine expression, an infiltrate composed of eosinophils, neutrophils, and mast cells, increase in serum IgE levels, and increased B cells in the draining lymph node.

These findings suggest that IL-18 (an IL-1R ligand) is a causative cytokine for the typical clinical and histopathologic features of the chronic phase of AD.²³

Rania and colleagues²⁴ recently published the results of a study including 20 atopic patients and 20 apparently healthy individuals serving as controls. Skin biopsies from all participants were examined for detection of IL-1 β and 33. Both cytokines were significantly highly expressed in atopics, which could explain a role of both of them in the pathogenesis of atopy and in the trafficking of leucocytes during the inflammation caused by AD. The IL-33 receptor, consisting of ST2 and IL-1 receptor accessory protein, was widely expressed as well, particularly by Th2 cells and mast cells. IL-33 is host protective against helminthic infection by promoting Th2-type immune responses. IL-33 can also promote the pathogenesis of asthma by expanding Th2 cells and mediates joint inflammation, AD, and anaphylaxis by mast cell activation.

IL-33 seems to drive Th2 responses, suggesting roles in allergic and atopic diseases, as well as in fibrosis. IL-33 exerts its effects by activating the suppression of tumorigenicity 2 (ST2)/IL-1aR receptor on different types of cells, including mast cells and Th2 cells. The ST2 receptor is either expressed on the cell surface or shed from these cells (soluble ST2, sST2), thereby functioning as a decoy receptor. After binding to its receptor, IL-33 activates NF- κ B, suggesting that it regulates the outcome of diseases such as AD.²⁵

In a study by Nutan and colleagues,²⁶ 45 subjects with AD were treated with betamethasone ointment and their IL-1 β levels were measured before and following treatment. The IL-1 β levels were increased in proportion to the severity of disease activity; following improvement they decreased in a statistically significant manner.

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