Role of Interleukin 1 in Atopic Dermatitis

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KEYWORDS

• Atopic dermatitis • Interleukin 1 • Inflammasome • T cells • Eczema • Mononuclear cells • 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-1α and IL-1β 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-1α and IL-1β.[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-κB) 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 colleagues[9] 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-κB 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-1α, and IL-1β 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-1α 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 colleagues[8] 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-1α	IL-1R1	IL-1RacP	Proinflammatory
IL-1β	IL-1R1	IL-1RacP	Proinflammatory
IL-1Ra	IL-1R1	NA	Antagonist IL-1α and β
IL-18	IL-18Rα	IL-18Rβ	Proinflammatory
IL-36Ra	IL-1Rp2	NA	Antagonist IL-36α, β, γ
IL-36α	IL-1Rp2	IL-1RAcP	Proinflammatory
IL-37	IL-18Rα	Unknown	Antiinflammatory
IL-36β	IL-1Rp2	IL-1RAcP	Proinflammatory
IKL-36γ	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.