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EDITORIAL

IL-36 RECEPTOR ANTAGONIST WITH SPECIAL EMPHASIS ON IL-38

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IL-36 is another family member of IL-1 and induces the production of proinflammatory cytokines and activates MAPK and NFκB pathways. IL-36 is a common mediator of innate and adaptive immune response and is inhibited by IL-36 receptor antagonist (RA). IL-36RA acts on IL-36 receptor ligand which exerts proinflammatory effect *in vivo* and *in vitro*. IL-38 binds to IL-36 receptor as does IL-36RA and has similar biological effects on immune cells. IL-38 is also a member of IL-1 cytokine and shares some characteristics of IL-1RA, binding the same IL-1 receptor type I. IL-38 plays a role in the pathogenesis of inflammatory diseases, exerting protective effect in some autoimmune diseases. Both IL-38 and IL-36RA have an anti-inflammatory biological effect, however in some cases have contrary effects.

"Biological response modifiers" are soluble factors (cytokines), a large and heterogeneous group that bind to cell surface receptors and which have diverse functions. Cytokines are secreted from cells to elicit their effects in an "autocrine" and "paracrine" manner, but also they can act in an "intracrine," non-secreted manner as nuclear factors. Cytokines regulate intercellular communication and play an important and essential role in the innate and adaptive immune responses (1-6).

IL-1α and IL-1β are pro-inflammatory cytokines which act through the binding of type I IL-1 receptor (IL-1RI). The IL-1 family of cytokines is composed of 11 different ligands, namely, IL-1α (also termed IL-1F1), IL-1β (IL-1F2), IL-1 receptor antagonist (IL-1RA or IL-1F3), IL-18 (IL-1F4), IL-1F5 to IL-1F10, and IL-1F11 (or IL-33). IL-1RA exerts an anti-inflammatory activity by binding IL-1RI (7-11).

Key words: IL-36, IL-38, cytokines, inflammation, immunity

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Table I. *Biological effects of IL-36.*

- Activates the MAPK and NF-kappaB pathways
- An important player in innate and adaptive immune response
- Pathophysiology of several diseases
- Initiation or regulation of immune responses and inflammation
- IL-1F5 (renamed IL-36RA) exerts receptor antagonist activities
- IL-1F5 inhibits NF-κB in certain cell types
- Mediates lesional psoriasis skin
- Mediates epidermis and dermis inflammation
- Mediates the proliferation of keratinocytes and in activate epithelial tissues
- Strongly increased in psoriatic-like mouse skin plaques
- IL-36α and IL-36β, but not IL-36γ, directly induced TNF-α
- IL-36 can be induced by Th17 cytokines
- Directly regulates IL-8 and IL-6
- Regulates the expression and enhance the function of Th17
- Interrelation with IL-22 in skin inflammation
- Mediate chronic kidney disease, and human rheumatoid synovial tissues

Table II. *IL-36RA activity.*

- Inhibits the production of IFN-γ, IL-4, and IL-17 by CD4(+) T cells and splenocytes
- Inhibits inflammatory skin lesions
- Inhibits psoriasis
- It is a natural antagonist of IL-36R
- Its antagonist activity is dependent upon removal of its N-terminal methionine
- The mechanism of IL-36RA antagonism is analogous to that of IL-1RA
- Reduces IL-8 production induced by IL-36γ
- Cause dose-response suppression of Candida-induced IL-22 and IL-17
- It has biological effects on immune cells by engaging the IL-36R
- Inhibits IL-36 receptor reducing Aspergillus-induced IL-17 and IFN-γ

IL-36 is a family member of interleukin-1 (IL-1), is produced by many different cells, activates MAPK and NF-kB pathways, and is a common mediator of both innate and adaptive immune responses (12-16) (Table I). During the past several years many papers have described a key role for IL-36 in psoriasis which is overexpressed in the skin of human plaque psoriasis (17-19). The inhibition of IL-36 with IL-36RA in human psoriatic skin has been found to ameliorate the inflammatory reactions (20-23). It has been shown that IL-22, IL-17A, and TNF-α induce the *ex vivo* production of all three IL-36 by human keratinocytes, whereas IFN-γ selectively induces IL-36β (24-26). In addition, IL-36α and IL-36β, but not IL-36γ, directly induce TNF-α mRNA and protein synthesis in keratinocytes demonstrating that IL-36α and IL-36β could regulate TNF-α directly (27-29). IL-36 induces the production of pro-inflammatory cytokines, including IL-12, IL-1β, IL-6, TNF-α, and IL-23 by dendritic cells with a more potent stimulatory effect than that of other IL-1 cytokines. IL-36 also induced the production of IFN-γ, IL-4, and IL-17 by CD4(+) T cells and cultured splenocytes, these stimulatory effects were antagonized by IL-

Table III. *IL-38 (IL-1F10) activity.*

- Member of the IL-1 family of ligands
- Gene located on human chromosome 2q13-14.1 near the IL-1RA gene
- Encodes 152-amino acid protein
- Shares between 41% and 43% amino acid identity with human IL-1RA
- Shares characteristics of the IL-1RA family
- It is expressed in heart, placenta, fetal liver, spleen, thymus, and human tonsil
- Role in inflammatory response and host defense
- Acts as an IL-1RA, and binds the same IL-1 receptor type I
- Binds to the IL-36R, as does IL-36RA
- Binding affinity of IL-38 is lower than that of IL-1RA and IL-1β
- It is involved in the regulation of immune responses
- It plays a role in psoriatic arthritis and ankylosing spondylitis
- It is protective in psoriasis
- Involved in increased number of lymphocytes Th17
- Involved in the high production of IL-17A, IL-21, and IL-22
- Plays a role in MAPK activation
- Reduces the production of *Candida*-induced IL-17 and IL-22
- Does not affect the production of Th1 cytokine IFN-γ
- Similar biological effects with IL-36RA
- Shares primary amino acid homology with IL-1RA and IL-36RA
- Does not bind IL-18R
- Decreases pro-inflammatory cytokines in PBMCs
- Increases pro-inflammatory cytokines in dendritic cells
- Has an inhibitory effect on Th17 cytokines

36RA (30).

IL-36R, is termed IL-1Rrp2 and its ligands are named IL-36α (IL-1F6), IL-36β (IL-1F8), and IL-36γ (IL-1F9); while IL-1F5, which has been shown to exert receptor antagonist activities, has been renamed IL-36RA. Therefore, these cytokines bind to IL-36R (IL-1Rrp2) and IL-1RAcP, activating similar intracellular signals as IL-1, whereas IL-36RA (IL-1F5) acts as an IL-36R antagonist (IL-36RA). IL-36(-α-β-γ) is highly expressed in epithelial tissues and skin which are exposed to pathogens and are also expressed abundantly in psoriasis (31-34).

These findings reveal that IL-36R ligands (IL-36α, IL-36β, and IL-36γ), exert pro-inflammatory effects and that IL-36RA acts as its antagonist (Table II). IL-36R agonist ligands are potent regulators of T-cell responses *in vitro* and *in vivo* and play an important role in innate and adaptive immune responses. IL-36 is expressed in dendritic cells and $CD4^+$ T cells and is able to stimulate the production of several cytokines in many different target cells, whereas IL-36RA exerts an inhibitory effect.

Results from different studies suggest that IL-36 is a pro-inflammatory cytokine and may be a mediator of both innate and adaptive immune responses (35-38). IL-36 receptor antagonist tocilizumab has an inhibitory effect on IL-36, and is effective in some patients with inflammatory diseases (39-42). In experimental animal, overexpression of IL-36α in keratinocytes exhibit inflammatory skin lesions, and this effect was less severe after IL-36RA–treatment *in vivo* (43-46). Taken together, these observations indicate that IL-36R ligands, including IL-36α, IL-36β, and IL-36γ, exert proinflammatory effects *in vitro* and *in vivo* and that IL-36RA acts as a natural antagonist. These pathways interact not only to

maintain cellular homeostasis and integrity but also to regulate inflammatory and autoimmune diseases.

IL-38 (IL-1F10)

IL-38 was cloned and characterized as a member of the IL-1 family of ligands in 2001 (47-51). The most recent addition to the ever-growing family of cytokines include interleukin-38 which was first identified by Haishan Lin and Bensen JT, et al. (52-56). These authors show that IL-38 is a member of the IL-1 family, in fact, the novel IL-1-like gene, IL-1F10, is located on human chromosome 2q13-14.1 near the IL-1 receptor antagonist gene (57-60). IL-1F10 cDNA encodes 152-amino acid protein that shares between 41% and 43% amino acid identity with human IL-1 receptor antagonist (IL-1RA). IL-1F10 shares characteristics of the IL-1RA family, including key amino acid consensus sequences and a similar genomic structure (61-65). IL-1F10 mRNA is expressed in several tissue such as heart, placenta, fetal liver, spleen, thymus, and activated B cells of the human tonsil (66-70). The expression in a variety of immune tissues and similarity to IL-1Ra suggest a role of IL-1F10 in the inflammatory response and host defense (52, 71-73).

Based on its amino acid homology to IL-1Ra, it has been reported that IL-38 acts as an IL-1RA, and binds the same IL-1 receptor type I (74-77). However, the binding affinity of recombinant IL-38 is significantly lower than that of IL-1RA and IL-1β (78-81). This newly discovered cytokine seems to act more as an immune regulator than a pro-inflammatory cytokine like other IL-1 family members. Therefore, it is involved in the regulation of normal immune responses. However, IL-38 plays a role in the pathogenesis of these inflammatory diseases such as psoriatic arthritis and ankylosing spondylitis (82-84), exerting a protective role in psoriasis (Table III). In these inflammatory and other autoimmune diseases the number of circulating lymphocytes T-helper 17 (Th17) is increased with high production of IL-17A, IL-21, and IL-22 (85-88). In fact, IL-38 plays a role in MAPK activation which is further enhanced by the stimulation through toll-like receptor, resulting in the enhanced pro-inflammatory cytokine production (89-92).

Recently, Dinarello et al. demonstrated that both IL-38 and IL-36RA reduce the production of *Candida*-induced IL-17 and IL-22 (93), confirming the anti-inflammatory effect of this new protein. This effect was absent on Th1 cytokine IFN-γ. However, how IL-38 modulates Th17 responses, is still unclear. It appears that IL-36Ra and IL-38 had similar biological effects on LPS-induced IL-6 in human DCs, however, neither IL-36Ra nor IL-38 performs as a typical receptor antagonist, like IL-1RA (94-97). Blocking the IL-36Ra or the IL-1R pathway mimicked the effects of IL-38 on the production of Th17 cytokines (98-102). It has been observed that IL-38 shares primary amino acid homology with IL-1Ra and IL-36Ra but is inconsistent with binding to the IL-18R (103-106). Some effects of IL-38 and IL-36RA remain unclear, for instance, why they decrease pro-inflammatory cytokines in peripheral blood mononuclear cells whereas increased pro-inflammatory cytokines in dendritic cells.

The effects of IL-38 are similar to those of IL-36RA but these two receptor antagonist do not behave as classic receptor antagonists like IL-1RA. Therefore, they are partial receptor antagonists and might act as agonists at higher concentrations. In addition, IL-38 provides evidence for binding to the IL-36 ligand-binding chain, and IL-1RA, IL-36RA, and IL-38 overlap in their ability to reduce IL-22 and IL-17 levels (107-110). Since IL-38 has an inhibitory effect on Th17 cytokines these findings may have important clinical and therapeutic implications and may represent novel targets for treatment. In conclusion, it is evident that IL-38 binds to the IL-36R, as does IL-36RA, and that IL-38 and IL-36RA have similar biological effects on immune cells through the IL-36 receptor.

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