Interleukin-22 and keratinocytes; pathogenic implications in skin inflammation

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Abstract

Interleukin (IL)-22 is produced from immune cells such as T helper (Th)22 cells, Th17/22 cells, and group 3 innate lymphoid cells. IL-22 signals via the IL-22 receptor 1 (IL-22R1) and the IL-10 receptor 2 (IL-10R2). As the IL-22R1/IL-10R2 heterodimer is preferentially expressed on border tissue between the host and the environment, IL-22 is believed to be involved in border defense. Epidermal keratinocytes are the first-line skin barrier and express IL-22R1/IL-10R2. IL-22 increases keratinocyte proliferation but inhibits differentiation. Aryl hydrocarbon receptor (AHR) is a chemical sensor and an essential transcription factor for IL-22 production. In addition, AHR also upregulates the production of barrier-related proteins such as filaggrin in keratinocytes, suggesting a pivotal role for the AHR-IL-22 axis in regulating the physiological skin barrier. Although IL-22 signatures are elevated in atopic dermatitis and psoriasis, their pathogenic and/or protective implications are not fully understood.

Keywords

IL-22, IL-22 receptor, aryl hydrocarbon receptor, skin barrier, keratinocyte, atopic dermatitis, psoriasis

Introduction

Interleukin (IL)-22 belongs to the IL-10-related cytokine family, which includes IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28 and IL-29 [1-3]. There is 79% homology between human and murine IL-22, and their respective genes are located on the same chromosome as interferon-γ (IFN-γ) [1-3]. The IL-22 receptor (IL-22R) is composed of a heterodimer of IL-22R1 and IL-10R2. The former protein is shared with the IL-20 and IL-24 receptor, while the latter is a component of the receptor for IL-10, IL-26, IL-28, and IL-29 [1-3].

Chronic inflammatory skin diseases such as atopic dermatitis and psoriasis bring about significant psychophysical and socioeconomic burdens to afflicted patients [4-8]. Recent therapeutic progress using biologics has demonstrated a critical pathogenic role for IL-4/IL-13-producing type 2 T helper (Th2) cells in atopic dermatitis and IL-17A-producing Th17 cells in psoriasis [4-8]. In addition to these essential axes, increased IL-22 signatures have been shown both in atopic dermatitis and psoriasis [9-14]. IL-22 is produced...
from specific acquired and innate hematopoietic cells, but its receptor, IL-22R1/IL-10R2, is preferentially expressed on non-hematopoietic cells such as epidermal keratinocytes [1-3]. Therefore, the physiological and pathological interaction between IL-22 and keratinocytes has gained particular attention from the viewpoint of skin barrier integrity and as a potential new target for the treatment of these inflammatory skin diseases [15, 16].

**Induction of IL-22 producing cells**

IL-22 is primarily produced by immune cells including CD4⁺ Th cells, CD8⁺ cytotoxic T (Tc) cells, natural killer T (NKT) cells, and group 3 innate lymphoid cells (ILC3) [1-3]. Non-lymphoid cells, including macrophages, neutrophils, mast cells, and fibroblasts may also produce IL-22, but production in keratinocytes does not occur [1-3, 15, 17]. Th and Tc cells are subdivided into several specialized subsets depending on surface markers, cytokine production and the expression of critical transcription factors as exemplified in Table 1 [18].

**Table 1. T cell subsets**

| T cell subsets | Surface markers | Cytokine production | Gene expression of critical transcription factors |
|---------------|-----------------|---------------------|-----------------------------------------------|
| Th1/Tc1       | CXCR3           | IFN-γ               | TBX21                                         |
| Th2/Tc2       | CCR4            | IL-4, IL-13, IL-5   | GATA3                                         |
| Th17/Tc17     | CCR4, CCR6      | IL-17A, IL-17F, IL-22 | RORC, TBX21                                  |
| Th17 + 1/Tc17 + 1 | CCR3, CCR6 | IL-17A, IFN-γ      | RORC                                          |
| Th22/Tc22     | CCR4, CCR6, CCR10 | IL-22, TNF-α     | AHR                                           |
| Tfh/Tfc       | CCR5            | IL-21               | BCL6                                          |
| CD4⁺Treg/CD8⁺Treg | CCR2, CCR4 | IL-10, TGF-β       | FOX3                                          |

Thf: T follicular helper; Tfc: T follicular cytotoxic; Treg: regulatory T; TGF: transforming growth factor

Among them, IL-22 is preferentially produced by Th22, ILC3, Th17 and to a lesser extent Tc22 and Tc17 cells [1-3, 18]. Although most IL-22-producing cells consist of IL-17A coproducing Th17/22 cells in mice, human IL-22 high-producers consist of Th22 cells that do not co-express IL-17A [1, 15, 19, 20]. Additionally, although human Th17 cells express CD161, Th22 cells do not [21]. ILCs, lacking antigen-specific T or B cell receptors, are divided into 4 subsets including ILC1 producing IFN-γ, ILC2 producing IL-13 and IL-5, ILC3 producing IL-17A and IL-22, and ILCreg producing IL-10 and TGF-β [1-3, 22, 23]. Almost all IL-22-producing cells, including ILC3, express CCR6, which recognizes only CCL20 (Table 1) [18, 24, 25]. Keratinocytes are a rich source of CCL20 [26, 27]; therefore, the CCL20/CCR6 axis may be important for the recruitment of Th22 cells in inflammatory skin diseases similar to that of Th17 cells [25, 28].

It is known that IL-22 production essentially depends on IL-23 [29, 30] and the aryl hydrocarbon receptor (AHR) [21, 31-33]. IL-23 (p19/p40) binds the IL-23R/IL-12Rβ1 heterodimer and activates the Janus kinase 2/tyrosine kinase 2 (JAK2/TYK2) and signal transducer and activator of transcription 3 (STAT3) pathway [34]. The IL-23-JAK2/TYK2-STAT3 axis appears to be crucial for IL-22 production in mice [29, 30], but may be dispensable in humans, as an IL-23 blockade profoundly decreased IL-17A but not IL-22 production [21].

AHR is a chemical sensor for various endogenous and exogenous ligands and serves as a cardinal transcription factor that promotes epidermal differentiation and barrier function [35-37]. The skin and intestinal tract are rich in AHR ligands produced from commensal microbiomes [32, 38-41]. Ultraviolet B (UVB) ray irradiation also generates high-affinity AHR ligands from tryptophan in the skin [42]. These AHR ligands are crucial for maturation of the host immune system against symbiotic commensal microbiomes via IL-22 induction [43]. In humans, AHR agonists reduce gene expression of the Th17 master transcription factor RORC without affecting TBX21, GATA3 and FOXP3 [21]. They also decrease the expression of IL-23R [21]. Importantly, AHR ligation not only decreases the number of Th17 cells but also primes naïve CD4⁺ T cells to produce IL-22 without affecting IL-17A or IFN-γ production, suggesting a pivotal role of AHR in developing Th22, but not Th17, cells in humans [21, 31] (Figure 1). In contrast, development
of both Th17 and Th22 cells is compromised in Ahr-deficient mice [33]. The number of IL-22-expressing ILCs is also markedly decreased in Ahr-deficient mice [32]. In addition to their potent activity towards Th22-prone immune deviation, AHR ligands can potentially upregulate the production of barrier-related proteins including filaggrin and loricrin, which enhance skin barrier integrity [35-37] (Figure 1).

It is intriguing that AHR is also an essential upstream transcription factor for IL-24 production in keratinocytes [44-46]. The relationship between AHR activation and IL-20 production is unknown thus far.

IL-4 and IL-13 are critical in the pathogenesis of atopic dermatitis [36], disrupting the barrier function of epidermal keratinocytes by downregulating the production of barrier-related proteins such as filaggrin and loricrin [37]. Barrier-disrupted keratinocytes produce large amounts of thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 [47-49]. These cytokines stimulate DCs to induce Th2-prone T cell differentiation [47, 50, 51]. Although this Th2-prone vicious cycle is predominantly active in atopic dermatitis [36], the lesional skin of atopic dermatitis patients harbors varying numbers of Th22, Th17 and Th1 cells, thus exhibiting marked endotype heterogeneity [52].

A possible explanation for Th22, Th17 and Th1 cell induction in atopic dermatitis is endothelin 1. Endothelin 1 is constitutively produced by keratinocytes [53]. Physiologically, it is preferentially expressed in basal keratinocytes [54, 55], but it is overexpressed to a variable extent in inflamed epidermis [54, 56]. Intriguingly, it is pruritogenic and induces pruritus in mice as well as humans [57]. As described above, DCs treated with TSLP, IL-25, or IL-33 induce Th2-dominant immune response [47, 50, 51]. In sharp contrast, DCs treated with endothelin 1 prompt T cells to differentiate towards Th22, Th17 and Th1 lineages [56]. Moreover, endothelin 1 inhibits Th2 cell differentiation [56]. Thus, endothelin 1 is one of the cutaneous factors promoting IL-22 production [56, 58]. In line with this notion, topical application of endothelin receptor antagonist alleviates not only mite-induced dermatitis [59] but also imiquimod-induced psoriasiform skin inflammation [60]. Notably, there is a mutual feedforward regulatory circuit between IL-25 and endothelin 1—IL-25 upregulates the expression of endothelin 1, while endothelin 1 also upregulates the production of IL-25 in keratinocytes [54].
IL-22R and IL-22 binding protein

IL-22 binds the IL-22R1/IL-10R2 complex [1-3] and stimulates the JAK2/TYK2 and STAT3 pathway [34]. Unlike other members of the IL-10 cytokine family, IL-22 has a soluble secreted receptor, the IL-22 binding protein (IL-22BP) [61-63]. IL-22BP exhibits a much higher affinity for IL-22 than IL-22R1 and therefore prevents the binding of IL-22 to IL-22R1 [64, 65]. DCs and T cells can produce IL-22BP [66, 67], while keratinocytes are a much richer source of functional IL-22BP [61]. Deficiency in IL-22BP aggravates skin inflammation [61].

IL-20, IL-22 and IL-24 use IL-22R1 for their receptor complexes [1-3]. Although IL-22 transmits signals via IL-22R1/IL-10R2, IL-20 and IL-24 can signal via IL-22R1/IL-20R2 as well as IL-20R1/IL-20R2 [68]. IL-20R2 and IL-10R2 are consistently expressed on the surface of cultured human keratinocytes regardless of confluence, passage number, or calcium levels in the medium [68]. In contrast, surface expression of both IL-20R1 and IL-22R1 is low in monolayer culture, and becomes high in 3-dimensional reconstituted human epidermis [68]. When IL-22R1-overexpressed keratinocytes are treated with 10 ng/ml of IL-20, IL-22 and IL-24, IL-22 induces the production of CCL20, CXCL8 and heparin-binding epidermal growth factor-like growth factor (HB-EGF) more potently than IL-20 and IL-24 [69]. Although T cells, B cells, NK cells and monocytes do not express IL-20R1 and IL-22R1 [68], functional IL-22R1 is known to be expressed on T cells from anaplastic lymphoma kinase-positive anaplastic large cell lymphoma patients [70].

IL-6 plays a critical role in the expression of IL-22R1 in keratinocytes because its expression is markedly decreased in IL-6-deficient mice [71]. MicroRNA-197 (miR-197) enhances the expression of IL-22R1 likely because it upregulates expression of the IL-6 receptor in keratinocytes [72, 73].

IL-22 and keratinocyte function

Many researchers have proposed a key role for IL-22 in epithelial border patrol especially in the intestinal tract, skin and airway [16, 74, 75]. The intestinal tract and its commensal and pathologic microbiomes maintain a homeostatic equilibrium with regard to host defense. IL-22 stimulates epithelial cells to produce antimicrobial peptides that are synergistically or additively upregulated in the presence of IL-17A [16]. IL-22 upregulates the production of CXCL1, CXCL5, CXCL9 and IL-6, which induce recruitment of relevant innate and acquired immune cells [16] (Figure 1). In addition, IL-22 induces the production of complement 3 from hepatocytes, which facilitates neutrophil killing of invading pathogens [74, 75]. Numerous AHR agonists are supplied to the intestinal tract from the diet and microbial metabolites which facilitate IL-22 production from intestinal IL-22-producing immune cells [76].

The skin is a body surface border, and epidermal keratinocytes are major cellular constituents of the host defense against the extracutaneous environment. UVB ray irradiation [42, 77], commensal microbiomes [40, 41] and environmental chemicals [78, 79] supply numerous AHR agonists to the skin. IL-22 stimulates keratinocytes to produce microbial peptides and chemokines such as S100A7, human β-defensin 2, human β-defensin 3 and CXCL8 [15, 16, 80-83] (Figure 1). However, the enhancing effect of IL-22 is relatively lower than other inflammatory cytokines [82, 84].

The expression of IL-22 is upregulated in their lesional skin of patients with atopic dermatitis and psoriasis [12-15]. IL-22 accelerates proliferation and migration of keratinocytes via STAT3 activation, and inhibits the terminal differentiation [69, 80, 85-87]. IL-22 blocks epidermal differentiation by inhibiting the expression of keratin 1 [80, 85, 86], keratin 10 [83, 88], involucrin [83, 86], loricrin [83, 88] and filaggrin [80, 83, 85, 87, 88]. In addition to STAT3 activation, IL-22-mediated downregulation of C/EBPα is also involved in the upregulation of proliferation and inhibition of differentiation in keratinocytes [89] (Figure 1). It is also known that IL-22- or IL-17A-treated keratinocytes increase their stemness by enhancing expression of CD29, CD44 and p63 [90].

House dust mites increase IL-22R1 expression and enhance the effects of IL-22 in keratinocytes [91]. UVB irradiation enhances the translocation of IL-22R1 from the cytosol to the membrane, and upregulates the responsiveness of keratinocytes to IL-22 [92]. IL-22 stimulates keratinocytes to produce IL-19, IL-20 and...
IL-24 [69]. IL-24 may also contribute to inhibit the expression of filaggrin via JAK1-STAT3 activation [69, 80, 93, 94] and to accelerate keratinocyte proliferation and S100A7 production [68].

Both IL-22 and IL-24 induce ROS production [95-97], while antioxidative AHR ligands may reduce the inflammatory action of IL-22 and IL-24. In fact, the antioxidant luteolin-7-glucoside alleviates ROS production and inhibits IL-22-mediated STAT3 activation [98].

However, IL-22 exhibits a beneficial effect on tight junctions. A recent study of bronchial epithelial cells demonstrated that IL-22 has the potential to reduce inflammation during influenza infection by enhancing tight junction activity [99]. Such protective function of IL-22 on tight junctions has been shown in keratinocytes in vitro, while IL-17A significantly downregulates tight junction expression in the epidermis [100].

**Conclusion**

IL-22 is produced from hematopoietic cells, and its receptor, IL-22R1/IL-10R2, is expressed on keratinocytes. Ligation of IL-22R1/IL-10R2 by IL-22 generally increases proliferation and inhibits differentiation of keratinocytes. This fundamental effect of IL-22 appears to work either as a pro- or anti-inflammatory depending on the type and timing of skin inflammation involved, but the precise physiopathological roles of IL-22 in the skin are not fully understood. Recent clinical studies have revealed that excess IL-22 in lesional skin may worsen atopic dermatitis, because the anti-IL-22 antibody fezakinumab shows a therapeutic potential for treating severe atopic dermatitis patients [11, 101]. Further clinical studies are necessary to explore the exact pathogenic implications of IL-22 in skin inflammation.

**Abbreviations**

AHR: aryl hydrocarbon receptor  
DCs: dendritic cells  
IFN-γ: interferon-γ  
IL: interleukin  
IL-22BP: IL-22 binding protein  
IL-22R: IL-22 receptor  
ILC3: innate lymphoid cells  
JAK2: Janus kinase 2  
STAT3: signal transducer and activator of transcription 3  
Tc: cytotoxic T  
Th: T helper  
TYK2: tyrosine kinase 2  
UVB: ultraviolet B

**Declarations**

**Author contributions**

Masutaka F wrote and Mihoko F revised the first draft. After English editing was performed, Masutaka F and Mihoko F agreed the final version and submitted the article.

**Conflicts of interest**

The authors declare no conflicts of interest.

**Ethical approval**

Not applicable.
Consent to participate
Not applicable.

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Not applicable.

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