

# Looking at Interleukin-22 from a New Dermatological Perspective: From Epidermal Homeostasis to Its Role in Chronic Skin Diseases

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## Keywords

Psoriasis · Atopic dermatitis · Hidradenitis suppurativa · Keratinocyte differentiation · 3D organotypic cultures

## Abstract

Twenty years after the cloning, characterization, and identification of interleukin (IL)-22 in 2000, the precise biological role of this cytokine in healthy and unhealthy skin is not completely known. The aim of this review is to provide an overview on the recent knowledge available in literature about the origin, sources, targets, molecular mechanism of action, and clinical issues regarding IL-22. Last but not least, recent experimental evidence obtained in a 3D model of organotypic culture of normal human skin highlights its homeostatic role and will be discussed in detail, as personal observations. As most of the data concerning IL-22 immunomodulating activity are obtained from mouse models, this work offers a new perspective on its clinical role. The hypothesis herein advanced is that IL-22 profoundly affects keratinocyte terminal differentiation, whereas, in order to induce a proliferation impairment, a more complex psoriatic-like microenvironment is needed.

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## Interleukin-22: Origins, Sources, Targets, and Molecular Mechanisms

Across the board of different cytokines able both to act on other immune cells and to instruct target cells, as interleukin (IL)-4 and IL-17, the role of IL-22 was poorly defined. As stated by Eyerich: “The function of IL-22 is difficult to generalize. It is not anti-inflammatory, nor it is necessarily proinflammatory” [1]. Depending on the context, IL-22 can exert protective functions in barrier defense, tissue repair, and homeostasis in various organs, including the skin [2], but its continuous and/or exacerbated action induces tissue inflammation, leading to immune disorders such as psoriasis [3].

In 2000, IL-22 march started with cloning, characterization, and identification originally as IL-10-related T-cell-derived inducible factor (IL-TIF) [4], and a 25% overall sequence identity between human IL-22 and IL-10 was reported [5]. It was later classified as a novel cytokine related to IL-10 [6], playing a key role in the homeostasis of mucosa and barrier organs [7].

During the first decade of this century, a more precise idea about the cellular sources of IL-22 has been taking

shape [8]. Previously considered as a T helper (Th) 1-associated cytokine [9], now IL-22 is recognized to have multiple origins. The main source is represented by specific T cells, such as CD4+, CD8+,  $\gamma\delta$  T cells [9, 10], and blood-derived natural killer (NK) cells, also called NK-22 [11]. A specific case is represented by type 3 innate lymphoid cells (ILCs), which express IL-22 following stimulation with IL-23 alone [12, 13]. Different CD4+ T cells are relevant producers of IL-22, namely Th17 and Th22, with the former releasing more IL-22 than Th1 cells [14], and a noteworthy difference exists between these T helper cells. Together with IL-22, Th17 also produces IL-17A and, for this reason, IL-17 and IL-22 have been linked together as the major secretory products of the Th17-cell subset. On the other hand, it has been demonstrated that a subpopulation of CD4+ T cells expressing IL-22, but not IL-17A, is present in the skin, strongly suggesting that, in humans, the secretion of the two cytokines is not necessarily associated. This new subset of T cells, named Th22 cells, is found mainly in tissues and produces IL-22 in response to IL-6 and tumor necrosis factor (TNF)-alpha [1, 15]. IL-22 production has been shown to be regulated also by IL-23, transcription factor ROR $\gamma$ t but mostly by aryl hydrocarbon receptor, from which IL-22 synthesis in Th17/22, Th22, and ILCs depends [5, 13, 16].

The bioactivity of IL-22 starts after its binding with the IL-22 receptor (IL-22R), a class II cytokine heterodimeric receptor consisting of two subunits, IL-22R $\alpha$  and IL-10R $\beta$ . Both chains are able to bind IL-22 independently, a unique feature compared with other receptors, and are required for the activation of intracellular signaling. While IL-10R $\beta$  is ubiquitously expressed and is found in many immune cells, IL-22R $\alpha$  is present almost exclusively on epithelial cells, including skin, pancreas, intestine, liver, eye, lung, and kidney, thus limiting and linking IL-22 responsiveness to the expression pattern of IL-22R $\alpha$  [17].

The binding of IL-22 to IL-22R, expressed in epithelial cells only, promotes in keratinocytes the activation of the receptor-associated Janus kinases JAK1 and Tyk2, followed by the phosphorylation of signal transducer and activator of transcription (STAT) 3 and, to a lesser extent, of STAT5 [18]. This intracellular signaling is involved in the vast majority of IL-22 functions and leads, finally, to keratinocyte proliferation and migration [19]. IL-22 signaling can also rely on a noncanonical and phosphotyrosine-independent pathway responsible for massive STAT3 activation. Recently, the specific abrogation of this noncanonical activation resulted in the resistance to the development of imiquimod-induced psoriasis in mice, with no effect on IL-22-dependent tissue repair or

barrier defense in organs other than skin [3]. Last but not least, the natural and soluble IL-22 receptor, IL-22-binding protein, antagonizes IL-22 activity in vitro by specifically binding IL-22 with high affinity [20].

## IL-22 and Skin

In vitro studies have demonstrated that IL-22 stimulation induces cell proliferation in normal human keratinocytes [21] and in HaCaT cells [22, 23]. After two IL-22 intradermal injections, acanthosis, i.e., thickening of the spinous layer, was evident in mouse skin [18]. Epidermal proliferation was also induced in diabetic mice [24] and transgenic mice engineered to overexpress IL-22 had aberrant skin phenotypes mimicking psoriasis [25, 26]. A psoriasis-like skin inflammation can be induced by subcutaneously injecting IL-23 or by painting the skin with the Toll-Like Receptor 7 agonist imiquimod [27].

However, the IL-22 contribution to cell processes other than proliferation and dealing with the fate of keratinocytes is established [28] and claims a particular clinical-oriented attention. One of the first pieces of evidence stems from the pioneering work of Boniface et al, in which the epidermal hyperplasia induced by IL-22 did not result from an increased basal keratinocyte proliferation but from the inhibition of keratinocyte differentiation [29]. Neonatal human epidermal keratinocytes incubated in a psoriatic microenvironment comprising IL-22, IL-17, and TNF-alpha showed a phenotypic behavior similar to that observed in psoriasis, in particular regarding the decrease of keratin 10 [30]. In 2021, Shou's group demonstrated a relationship between Th22/Th17 responses and lipid oxidation leading to ferroptosis, a new type of programmed cell death involved in psoriasis [31]. In parallel, the lack of IL-22 affects the skin homeostatic balance as shown by the impairment of cutaneous wound healing in IL-22<sup>-/-</sup> mice after full-thickness wounding [32]. After the topical application of imiquimod, the psoriasiform-like skin appearance is almost completely absent in IL-22-deficient mice or in mice treated with a specific IL-22 blocker [33]. Table 1 reports the implication of IL-22 on skin homeostasis.

Human epidermis, as a stratified squamous keratinized epithelium, exhibits a finely-tuned stratification in which keratinocytes represent the predominant cytotype (Fig. 1a, b) and Langerhans cells, i.e., the first-line defense of the skin, are intermingled in the lowermost less differentiated layers (Fig. 1a, c). In our laboratory, in the last decade, the standardization of a 3D organotypic culture

**Table 1.** IL-22 implication on skin homeostasis

Cited reference	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[29]	[32]	[33]	[30]	[31]	[37]
Process	Cell proliferation in mouse skin after IL-22 injection	Cell proliferation in HaCat cells after IL-22 incubation	Cell proliferation in HaCat cells after IL-22 incubation and curcumin	Wound healing in diabetic mice after IL-22 injection	IL22 <sup>-/-</sup> mice	Transgenic overexpressing IL-22 mice	Psoriasis induction in IMQ/IL-23 injection	Keratinocyte differentiation in RHE after IL-22 incubation	Wound healing in IL22 <sup>-/-</sup> mice	Psoriasis-like lesions after IMQ application	K10 expression in neonatal NHEK incubated with IL-22, and TNF-alpha	Inhibition of ferroptosis in mouse skin after IMQ application	K10 expression in a 3D model of normal human skin
Evidence	Thickening of the spinous layer/acanthosis	Stimulation of cell proliferation	Inhibition of cell proliferation	Acceleration	Inhibition of acanthosis	Induction of acanthosis and loss of granular layer	Psoriasis-like skin	Epidermal hyperplasia	Delay	Absence of scaly lesions	Psoriatic phenotype	Suppression of IL-22 expression	Inhibition of cell differentiation

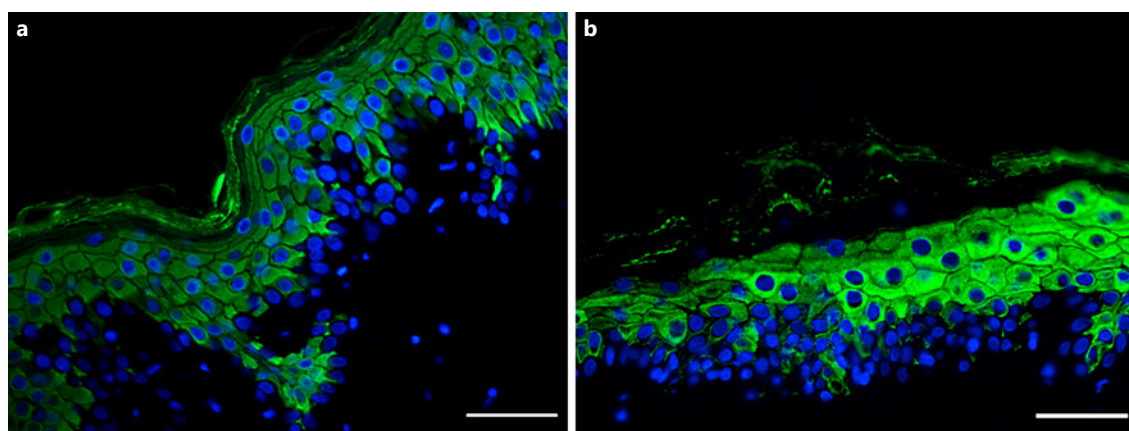
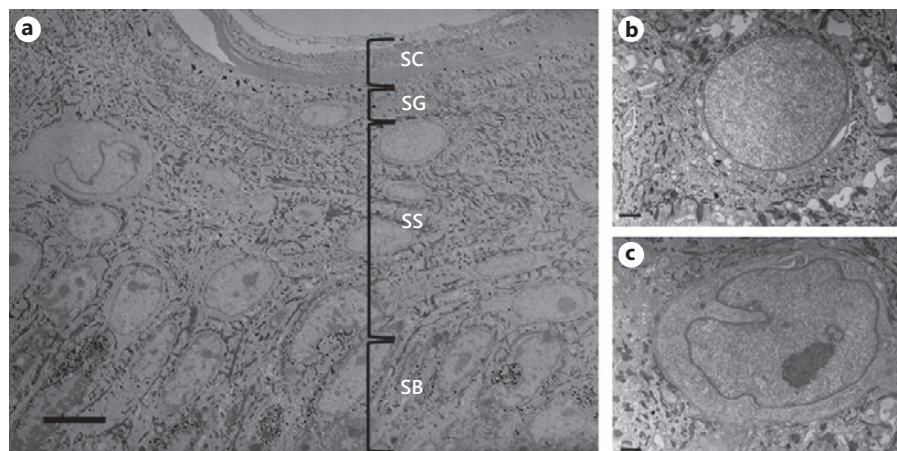
IL-17, interleukin-17; IL-22, interleukin-22; K10, keratin 10; IMQ, imiquimod; NHEK, normal human epidermal keratinocytes; RHE, reconstituted human epidermis; TNF-alpha, tumor necrosis factor alpha.

**Table 2.** IL-22 implication on skin disorder

Cited reference	[44]	[45]	[47]	[48]	[50]	[51]	[52]	[53]	[54]	[63]	[64]
Methods	UV phototherapy in psoriatic patients	Serum samples from psoriatic patients	Skin lesions of psoriasis vulgaris	Skin lesions of psoriasis vulgaris	Skin lesions of psoriasis vulgaris	Skin lesions of moderate-to-severe psoriasis vulgaris	IL-22 neutralizing antibodies in a mouse model of psoriasis-like inflammation	Prevention of IL-22-induced STAT3 activation in IMQ-treated mice	Skin lesions of moderate-to-severe psoriasis	Skin biopsies and peripheral blood from chronic AD patients	Skin lesions of patients with chronic plaque psoriasis and IL-22 application in mice
Results	Decrease of IL-22 serum concentration and correlation with clinical severity	Elevation of IL-22 serum concentration	IL-22 mRNA upregulation in psoriatic lesions	IL-22 mRNA upregulation in psoriatic lesions	Downregulation of IL-22BP expression in psoriatic plaques	Increase of IL-22 expression and downregulation of IL-22BP expression in psoriatic plaques	Prevention of psoriatic plaque formation	Resistance to the development of dermatitis	Upregulation of chemokines and antimicrobial peptides production	Correlation between IL-22+CD8+ T-cell frequency and AD disease severity	Association between high IL-22 levels in psoriatic skin and upregulation of antimicrobial peptides

IL-17, interleukin-17; IL-22, interleukin-22; IL-22BP, interleukin-22 binding protein; IMQ, imiquimod; TNF-alpha, tumor necrosis factor alpha; UV, ultraviolet rays.

**Fig. 1.** Transmission electron microscopy photomicrographs of normal human skin. **a** Epidermal stratification. SC, stratum corneum; SG, granular layer; SS, spinous layer; SB, basal layer. **b** Spinous layer keratinocyte. **c** Langerhans cell. Bars, 5  $\mu\text{m}$  (**a**); 1  $\mu\text{m}$  (**b**, **c**).



**Fig. 2.** Expression of keratin 10 in normal human skin (**a**) and after 24 h of incubation with IL-22 (**b**) in a Transwell system at the air-liquid interface. Bar, 50  $\mu\text{m}$ .

model of normal human skin [34], because of the similarity to the physiological condition, allowed to dissect precisely the epidermal response induced by different proinflammatory cytokines [35, 36]. A single stimulation with IL-22 early impairs keratinocyte maturation as regarding keratin 10 expression (Fig. 2), without affecting keratinocyte proliferation [37]. On the other hand, other proinflammatory cytokines, alone or in combination, exerted an antiproliferative effect in the same experimental setting [35]. A very recent study reported that JAK1 was also specifically expressed after IL-22 incubation and was followed by an increase in pSTAT3/STAT3 ratio [38], in accordance with the induction of keratin 17 in the spinous layer reported previously [37].

Considering the high potential of extrapolating these findings to the physio-pathological condition, we advance the hypothesis that, in normal human epidermis, IL-22 primarily exerts a homeostatic role. IL-22 pro-

foundly affects keratinocyte terminal differentiation, whereas, in order to induce a proliferation impairment, a more complex psoriatic-like microenvironment is needed.

Although the etiopathogenesis of psoriasis and atopic dermatitis (AD) is profoundly different, the increase of IL-22 levels is a common feature and, for this reason, its relevance in both diseases will be discussed. The implication of IL-22 on skin disorders is summarized in Table 2.

### IL-22 and Psoriasis

Psoriasis is characterized by erythematous, scaly plaques mainly on extensor surfaces and, especially in its more severe forms, by a very low quality of life. In the past, it was considered mainly as a hyperproliferative disorder of keratinocytes with no immunological implica-

tions. In the last few decades, thank to basic studies and to the introduction of biologics for the treatment of moderate-severe clinical forms of psoriasis, the role of the immune system in its pathogenesis has become dominant [39]. Due to the implication of both innate and adaptive immune responses, psoriasis is classified as an immune-mediated inflammatory disease. The paradigm of a Th1-driven disease has been overcome by the discovery of IL-23/Th-17 axis in the pathophysiology of psoriasis. Among the many T-cells circulating in psoriatic patients, Th22, Th1, and Th17 are increased [40] and their pathways can be downregulated by treatment with anti-TNF- $\alpha$  treatment [41]. Standing in continuation with these clinical observations, in the 3D organotypic culture model of normal human skin, the psoriatic shift induced by IL-17 was promptly reverted by a specific anti-IL-17A agent and the early cellular mechanisms involved in such an effect were elucidated [42]. On the other hand, the anti-IL-17A antibody secukinumab, effective in the treatment of psoriasis, did not affect AD progression, suggesting that IL-22 may exert pathogenic effects beyond those involving Th2 cytokines [43]. Psoriatic patients have high IL-22 levels and the levels of IL-22 correlate with the severity of the disease, as proven by PASI score [44, 45] and specific treatment lowers it [46]. In psoriatic lesional skin, IL-22 mRNA is positively expressed [47, 48] and high levels of IL-22 are found. Moreover, the expression of the receptor of IL-22 is increased in psoriatic skin and the expression of IL-22 receptor, as well as its distribution, correlate with the severity of the disease [49]. The limited presence of IL-22-binding protein, i.e. the natural IL-22 inhibitor, supports inflammation in psoriatic skin [50], and its expression was downregulated in skin biopsies of psoriatic patients compared to the skin of healthy donors [51].

In a mouse model of psoriasis-like skin inflammation, IL-22 is required to induce and sustain Th-17 response [52], suggesting that IL-22 antagonism might be a promising therapy for the treatment of psoriasis, but possible side effects of anti-IL-22 antibodies on the gut should not be under evaluated. As STAT3 is known to mediate deleterious effects in the development of psoriasis [26], a recent study indicated that preventing IL-22-induced STAT3 alternative activation “with a light touch” could be able to block the deleterious effects of IL-22 while leaving intact the beneficial ones [53].

It is also well established that IL-22 is able to upregulate a group of proinflammatory molecules, CXC-chemokine ligands (CXCLs), and PDGF4, but above all, it downregulates genes associated with keratinocyte terminal differentiation [54, 55]. Furthermore, the early onset of the

disease has been correlated with a high-risk haplotype in the IL-22 promoter that determines enhanced production of IL-22 [16].

## IL-22 and AD

AD is associated with a wide burden and is characterized clinically by heterogeneous skin lesions varying a lot according to the age of onset and to disease progression with a very disabling symptom: pruritus [56]. While most cases of AD occur in early childhood, mostly presenting a recurrent and chronic course that often resolve prior to puberty, in up to half of patients it may persist into adulthood, becoming a lifelong condition. Both altered immunoresponses and barrier defects are key actors of its pathogenesis [57]. Proteins contributing to the functional epidermal barrier as filaggrin, loricrin, and involucrin are all decreased in lesional and non-lesional skin of AD [1, 29, 58]. The consequent epidermal barrier dysfunction causes the increased colonization of bacteria such as *Staphylococcus aureus* [59, 60]. In some phenotypes of AD, there is a genetic mutation of filaggrin [61], lacking in others, thus suggesting that filaggrin mutation only partly explains filaggrin downregulation in AD.

According to the old paradigm of Th1/Th2 polarization, in which AD was considered a type Th2 skin disease, quite recent research has revised this paradigm and, even if AD is dominated by type Th2 helper and type 2 ILCs, other immunopathogenetic pathways seem to play a role [62]. A study by Nogral et al. demonstrated that, by analyzing lymphocytes directly isolated from skin biopsies or peripheral blood of chronic AD and psoriasis patients, AD skin had upregulated expression of IL-22, independent from Th17 cells. CD4+T and CD8+ T-cells populations were increased in AD skin and IL-22-producing CD8+ T-cell frequency correlated with AD disease severity [63].

While the implications of IL-22 have been extensively studied in the pathogenesis of two common chronic inflammatory skin diseases as AD and psoriasis, we are willing to address another chronic relevant, often underdiagnosed, skin disease: hidradenitis suppurativa (HS). IL-22 has many effects on keratinocytes together with its differentiative action as it can also induce keratinocytes to produce (i) antimicrobial proteins, including  $\beta$ -defensin 2,  $\beta$ -defensin 3, S100A7, S100A8, S100A9, and lipocalin 2 [29], (ii) neutrophil-attracting chemokines, such as CXCL1, CXCL2, CXCL5, and CXCL8, and can inhibit the expression of CCL22, attracting Th17 and Th2 [26]. IL-22 can also induce the expression of extracellular matrix-de-

grading enzymes matrix metalloproteinases 1 and 3, which are required for epithelial migratory capacity during epithelial repair as it happens in defined steps of HS [64]. The defective function of keratinocytes in HS has been demonstrated through an in vitro scratch assay: keratinocytes from HS, at variance with normal keratinocytes and keratinocytes from chronic wounds, exhibited significantly lower amounts of IL-22 (8.01 pg/mL) compared to normal and chronic wound keratinocytes, suggesting that defects in IL-22 signaling may play a role in HS pathogenesis [65]. The immune activation in HS, demonstrated through the upregulation of 129 genes, is significantly higher in lesional HS skin as compared to the skin of healthy controls including proinflammatory cytokines (IL-1 $\alpha$ , IL-6, TNF- $\alpha$ ), IL-17-associated cytokines (IL-17A, IL-17F, IL-23A), the IL-10 family of cytokines (IL-10, IL-19, IL-20, IL-22, IL-24), and IFN family members (IFNA1, IFNB1, IFNG, IL-12B), further supporting the role of a heterogeneous group of cytokines in the pathogenesis of HS and well explaining the opportunity for targeted therapies [66]. On the other hand, IL-22 serum levels in HS patients are lower than in controls (independent of the severity of the disease) and this decrease correlates with decreased levels of hepcidin, which is one of the regulators of iron storage [67]. Rosi et al. [68] have recently reported a deficiency of IL-22 in lesional HS skin compared to psoriatic lesional skin and this reduction was not linked to a reduced T cell infiltration but to a high expression of IL-10 in HS lesions.

## Conclusions

According to data from the literature and from our 3D skin model, the role of IL-22 in chronic inflammatory disease as psoriasis and AD is better highlighted. The in-

crease of upregulating proinflammatory molecules induced by IL-22, as discussed above, is a key step in the pathogenesis of both skin chronic inflammatory diseases. Further studies are necessary in order to establish which clinical step better correlates with IL-22 increase to better tailor biological treatment.

## Key Message

IL-22 impairs keratinocyte terminal differentiation in normal human epidermis, exerting a homeostatic role.

## Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Author Contributions

Elena Donetti wrote the first draft and described the origins, sources, targets, and molecular mechanisms of IL-22, and its impact on skin homeostasis. Francesca Prignano revised the draft and described the involvement of IL-22 in psoriasis, AD, and HS.

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