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REVIEW ARTICLE

Role of IL-22 in homeostasis and diseases of the skin

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Interleukin-22 (IL-22) is a cytokine mainly produced by T cells and innate lymphoid cells (ILC). IL-22 primarily targets non-hematopoietic cells such as epithelial cells and fibroblasts. In the skin, IL-22 promotes the proliferation of keratinocytes and dermal fibroblasts. IL-22 furthermore regulates innate immune responses as it induces the production of antimicrobial proteins and neutrophil-attracting chemokines. IL-22 plays an important role in wound healing and in the protection against skin infections. However, IL-22 can also contribute to the pathogenesis of several inflammatory skin diseases such as psoriasis, atopic dermatitis and allergic contact dermatitis. In this review, current information regarding the structure, function and regulation of IL-22 is discussed with a special focus on the role of IL-22 in the skin and in skin diseases.

Key words: Cytokine; interleukin-22; IL-22 receptor; skin; inflammatory skin diseases; immunology.

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INTRODUCTION

Interleukin-22 (IL-22) belongs to the IL-20 subfamily of the large IL-10 family that, in addition to IL-22, includes IL-10, IL-19, IL-20, IL-24, IL-26, IL-28A, IL-28B and IL-29 [1]. IL-20 subfamily cytokines primarily act on epithelial cells and help maintain tissue integrity and restore homeostasis of epithelial layers during wound healing activities [1]. Additionally, IL-22 and other IL-20 subfamily cytokines induce the production of antimicrobial peptides that protect these cells from various pathogens [2]. In 2000, the *il22* gene was identified in mouse T cells and was originally named IL-10-related T cell-derived inducible factor (IL-TIF) due to the homology with IL-10 [3]. IL-22 is mainly produced by T cells and ILC [4,5]. In the skin, the IL-22 receptor (IL-22R) is expressed by keratinocytes and dermal fibroblasts [6]. Thus, IL-22 facilitates the communication between leukocytes and skin cells, thereby enhancing tissue repair processes and defence mechanisms in the skin.

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CELLULAR SOURCES AND REGULATION OF IL-22 PRODUCTION

Several types of immune cells can produce IL-22. The most well-described cells to produce IL-22 are $CD4^+$ T cells, but other cells, such as ILC type 3 (ILC_3), natural killer (NK) cells, $CD8^+$ T cells, $\gamma\delta^+$ T cells and dendritic cells (DC), also have the ability to produce IL-22. IL-22 production is dependent on stimulation of the cells by various cytokines and the activation of specific transcription factors, which are listed in Table 1 and described in the following sections.

Early studies found that IL-22 was secreted by mouse T lymphocytes in response to IL-9 [3]. Later, it was found that Th17 cells, in addition to producing its signature cytokine IL-17, also produced significant amounts of IL-22 [7]. Despite IL-17 and IL-22 were reported to be co-secreted from Th17 cells, these cytokines were regulated differently. The cytokines IL-6, IL-1β and TGFβ are essential for the development of IL-17-producing Th17 cells. Furthermore, the addition of IL-23 led to the concomitant production of IL-22 from these cells [8]. Another study found that TGFβ induces IL-17

Table 1. Factors involved in promoting or inhibiting IL-22 in various immune cells

Cell type	Species	Promoting factors	Inhibiting factors	Transcription factors involved	References
$CD4^+$ αβ T cell	Human	IL-1β IL-6 IL-23 TNF AhR agonist TGFβR inhibitor	AhR antagonist RORγt inhibitor Vitamin D	AhR RORγt VDR	[4]
	Human	IL-1β IL-23 IL-6 AhR agonist	AhR siRNA RORγt siRNA	AhR RORγt	[14]
	Human	TNF IL-6			[13]
ILC_3	Mice	IL-1β IL-23 RA		RORγt RAR	[15]
	Human	IL-23		AhR RORγt	[16]
NK cells	Human	IL-23		AhR RORγt	[17]
	Human	IL-1β IL-23		AhR RORγt	[20]
$γδ^+$ T cells	Mice	IL-1β IL-18 IL-23 RA	RAR inhibitor	RORγt RAR	[15]
	Mice		AhR antagonist	AhR	[56]

production whilst inhibiting IL-22 production in Th17 cells [9]. This differential regulation of IL-17 and IL-22 was substantiated by investigating the transcription factors that regulate IL-17 and IL-22 production in Th17 cells. A central regulator of IL-22 production was the aryl hydrocarbon receptor (AhR), and IL-22 production was less dependent on the retinoic acid receptor (RAR)-related orphan receptor gamma (RORγt) [10]. In contrast IL-17 production was highly dependent on RORγt [11]. In 2009, a sub-population of memory $CD4^+$ T cells was defined as Th22 cells that produced high amounts of IL-22 with little or no IL-17 and IFNγ [12,13]. This cellular subset expressed among others the skin-homing chemokine receptors (CCR)4, and CCR10, indicating that Th22 cells and IL-22 could play a central role for skin homeostasis and inflammation [12-14].

Subsequently, studies have tried to identify which cytokines and transcription factors that regulate the differentiation of Th22 cells *in vitro*. One study found that IL-6 and TNF were important for IL-22 production [12]. Another study reported that IL-1β plus IL-23 constituted the optimal cocktail for Th22 differentiation and that AhR and RORγt were the key transcription factors for IL-22 secretion [14]. In accordance, a recent study demonstrated that inhibition of AhR and RORγt signalling reduced IL-22 production in Th22 cells [4]. This study also found that the presence of IL-6, TNFα, IL-1β, IL-23, AhR agonist (FICZ) and TGFβ receptor (TGFβR) inhibitor (galunisertib) constituted the optimal condition for the differentiation of Th22 cells *in vitro*.

In addition to $CD4^+$ T cells, IL-22 can also be produced by $γδ^+$ T cells [15], ILC_3 [15,16] and NK cells [17]. IL-22-producing ILC_3 residing in the skin and gut epithelium underscores that IL-22 likely plays a role in homeostasis of these tissues [5]. Interestingly, as IL-22-producing T cells, ILC_3 expresses RORγt and AhR that modulate the production of IL-17 and IL-22 [18,19]. Accordingly, IL-23 enhanced the development of IL-22-producing ILC_3 [19]. In line with this, NK cells expressing IL-22 (NK22) express both AhR and RORγt [17], and IL-22 production from NK22 cells increased in the presence of IL-1β and IL-23 [20].

TGFβ and signalling from the TGFβR affects IL-22 production. TGFβ is known for its involvement in $CD4^+$ T cell differentiation, where it affects differentiation in a concentration-dependent manner. Whereas high amounts of TGFβ are required for the generation of regulatory T cells (T_{reg}), lower amounts of TGFβ enhance Th17 cell differentiation [9]. *In vitro* studies of Th17 cells have suggested that TGFβ inhibits IL-22 production [8]. This is in line with studies demonstrating that inhibition of

TGFβR signalling enhanced the production of IL-22 in both mouse [21] and human $CD4^+$ T cells [4,13]. However, another study found that TGFβR signalling enhanced IL-22 production in Th17 cells [22]. Thus, further studies are required to fully understand the role of TGFβ and TGFβR signalling in IL-22 production.

AhR is involved in IL-22 regulation. AhR is a cytoplasmic receptor that is activated by exogenous and endogenous molecules [23]. Several studies have reported that AhR signalling plays a key role in the differentiation and function of $CD4^+$ T cells [9,10,12,14]. It has recently been reported that AhR controls IL-21-induced IL-22 production in murine $CD4^+$ T cells in a STAT3-dependent manner [24]. In addition, AhR activity promoted the development of Th17 cells and induces IL-22 production from these cells [9]. In line with this, several studies have identified AhR as a key transcription factor controlling IL-22 production in Th22 cells and $\gamma\delta^+$ T cells [4,12,13,14].

Vitamin D_3 is well-known for its immunomodulatory actions, and studies have elucidated the modulating role of vitamin D_3 on T cell differentiation [25]. Recent studies have explored the effect of vitamin D_3 on IL-22-producing cells such as Th17 and Th22 cells. It was found that vitamin D_3 increased the secretion of TNF, IL-6, IL-1β and IL-23 from dendritic cells (DC) leading to augmented IL-22 secretion from $CD4^+$ T cells [26]. In line with this, other studies found that vitamin D_3 enhances plasmacytoid's (pDC) ability to promote Th22 differentiation [12]. In contrast, another study demonstrated that the vitamin D_3 analogue, calcipotriol, inhibited IL-22 production in human Th17 cells [27]. This is in good agreement with a recent study, which found that vitamin D_3 inhibited IL-22 expression and secretion. This study identified a repressive vitamin D-responsive element (VDRE) in the *il22* promotor allowing for a direct inhibition of IL-22 production by the active form of vitamin D_3 [4]. Consequently, vitamin D_3 may be considered as a potential therapeutic to modulate IL-22-driven disorders. The vitamin A metabolite retinoic acid (RA) also regulates IL-22 production. However, in contrast to vitamin D, RA upregulates transcription of the *il22* gene [15].

Toll-like receptor (TLR) signalling has also been reported to induce IL-22 production. This can either be due to a direct, IL-23-independent effect of TLR4 and TLR9 ligands on bone-marrow-derived DC [28] or an indirect, IL-23-dependent effect of TLR5 and TLR7/8 ligands on lamina propria DC [29] and cells in the skin [30], respectively. TLR7/8 ligands also indirectly increase IL-22 production in the skin by stimulating IL-36 production in the keratinocytes [31].

In addition to the factors that regulate IL-22 production in immune cells described above, a cell-extrinsic factor that regulates IL-22 function exists. This is the IL-22-binding protein (IL-22BP), which strongly binds IL-22 and thereby controls the bioavailability and activity of IL-22 [32]. IL-22BP has high homology with the IL-22R1 chain of the IL-22R; however, IL-22BP binds IL-22 with much higher affinity compared with the IL-22R1 subunit [32], explaining its sequestering effect on IL-22. IL-22BP is secreted by both immune cells and epithelial cells [33]. During homeostasis, IL-22BP is highly expressed in immature DC and keratinocytes, and IL-22BP is thought to neutralize the effects of IL-22. In DC, IL-22BP expression is controlled by the inflammasome and RA [33,34]. During acute inflammation and tissue damage, DC become activated and the activation of the inflammasome results in the inhibition of IL-22BP secretion [34]. Thus, the bioavailability of IL-22 increases, allowing IL-22 to mediate tissue repair at the epithelium. Furthermore, it has been reported that deletion of the IL-22BP gene results in exacerbated and uncontrolled skin inflammation [35].

In summary, $CD4^+$ and $CD8^+$ T cells, $\gamma\delta^+$ T cells, NK cells and ILC_3 represent sources of IL-22. Various cytokines are involved in IL-22 regulation. These include IL-1β, IL-6, IL-7, IL-18, IL-21, IL-23, TGFβ and TNF. Furthermore, the transcription factors AhR, RORγt and STAT3 play essential roles in regulating *il22* transcription. Furthermore, vitamin D_3 and vitamin A also modulate IL-22 expression and lastly IL-22BP controls the bioavailability of IL-22 (Fig. 1).

STRUCTURE EXPRESSION AND FUNCTION OF THE IL-22 RECEPTOR

The IL-22R is a heterodimer consisting of the IL-22R1 and the IL-10R2 chains [36] (Fig. 2). IL-22 binds with high affinity to the extracellular part of the IL-22R1 chain [37]. It is believed that IL-22 binding to IL-22R1 leads to a conformational change that enhances binding of the IL-22-IL-22R1 complex to the IL-10R2 chain [37]. Whereas the IL-10R2 chain is ubiquitously expressed, the IL-22R1 chain is mainly expressed by epithelial cells and fibroblasts located in the skin, intestine, lung, liver, kidney and pancreas [6].

Binding of IL-22 to the IL-22R activates several intracellular signalling pathways most importantly the JAK/STAT pathway [38] (Fig. 2). Thus, IL-22 binding to the IL-22R results in the activation of JAK1 and TYK2 that phosphorylate specific tyrosine residues in the cytoplasmic tail of the IL-22R

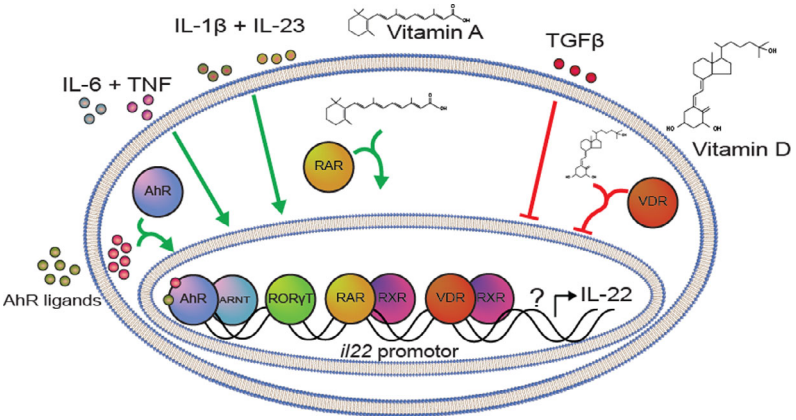

Fig. 1. Proposed model for IL-22 gene regulation. Various cytokines and other factors affect *il22* expression and IL-22 secretion. Some of these factors upregulate IL-22 levels, whereas others are seen to downregulate IL-22. The cytokines IL-6, TNF, IL-1β and IL-23 have all been shown to increase IL-22 levels. This is possibly due to their actions in upregulating the activity of the transcription factor, RORγt, that can directly bind to the promoter region of the *il22* gene and mediate transcription. Furthermore, the activity of the transcription factor, AhR, has also been found to regulate IL-22 expression and production. Thus, ligands that bind and activate AhR (such as the AhR agonist, FICZ), lead to increased IL-22, whereas inhibition of AhR activity (such as with the AhR antagonist, CH-223191) leads to decreased IL-22 levels. Additionally, vitamin A has been shown to augment IL-22 production. Upon binding to the RAR, the complex translocates to the nucleus, where it together with RXR forms a complex that can upregulate expression of the *il22* gene. Other factors inhibit IL-22 levels. Signalling by TGFβ through the TGFβ receptor has been found to decrease IL-22 levels. Furthermore, it has recently been shown that vitamin D_3 exerts an inhibitory effect on IL-22. This is due to the presence of a negative vitamin D-response element (VDRE) in the promotor-region of the *il22* gene. Upon interaction between vitamin D_3 and VDR, this complex translocates to the nucleus, where it together with RXR forms a heterodimer that can downregulate expression of the *il22* gene and consequently IL-22 secretion is inhibited. Furthermore, there is most likely also other regulatory factors of IL-22, which is indicated by the question mark in the figure. AhR, aryl hydrocarbon receptor; ARNT, AhR nuclear translocator; RAR, retinoic acid receptor; RORγt, RAR-related orphan receptor γ; RXR, retinoid X receptor; TGFβ, transforming growth factor β; TNF, tumor necrosis factor; VDR, vitamin D receptor.

chains. The phosphorylated IL-22R chains attract STAT3 molecules, which are then phosphorylated by the activated JAK1. STAT3 phosphorylation induces the formation of STAT3 homodimers that translocate to the nucleus where they regulate expression of STAT3-responsive genes. In addition to STAT3, STAT1 and STAT5 play a role in IL-22R signalling, although to a lesser extent than STAT3 [38]. Other signalling pathways than the JAK/STAT pathway are also activated by IL-22. These include the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway and the mitogen-activated protein kinase (MAPK) pathways (ERK1/2, Jun N-terminal kinase (JNK) and p38 kinase [38] (Fig. 2).

IL-22 IN SKIN HOMEOSTASIS, WOUND HEALING AND INFLAMMATION

The skin is a highly specialized organ, and the keratinocytes play vital roles for a functional skin barrier and the defence against various environmental microbes and chemicals. IL-22 affects keratinocytes' functions as it inhibits the production of several proteins involved in terminal keratinocyte differentiation such as keratin 1 and 10 (KT1/10), involucrin, profilaggrin, loricrin and desmocollin [39-41]. Thus, IL-22 affects keratinocyte proliferation, migration and maturation [42]. IL-22 has also been shown to aid wound healing processes [41,43]. A study found that IL-22 was upregulated upon wounding in a mouse model, and as a result, keratinocyte differentiation was inhibited [41]. Furthermore, lack of IL-22 in mice led to major defects in wound healing processes [43]. In this study, IL-$22^{-/-}$ mice exerted severely impaired wound healing, but this could to some extent be rescued by exogenous addition of recombinant IL-22. Moreover, studies have found that IL-22 induces the expression of anti-apoptotic genes (e.g. Bcl-2 and Bcl-xl) and matrix metalloproteinases (e.g. MMP1/3) that enhance cell proliferation, remodelling of the epidermis and tissue repair mechanisms [39,41].

In addition to affecting the keratinocytes during wound healing, IL-22 enhances the antimicrobial responses of the keratinocytes through the induction of antimicrobial peptides such as β-defensins 2/3, SA1007, 1008, 1009 and lipocalin-2 [39]. Furthermore, IL-22 stimulates keratinocytes to release

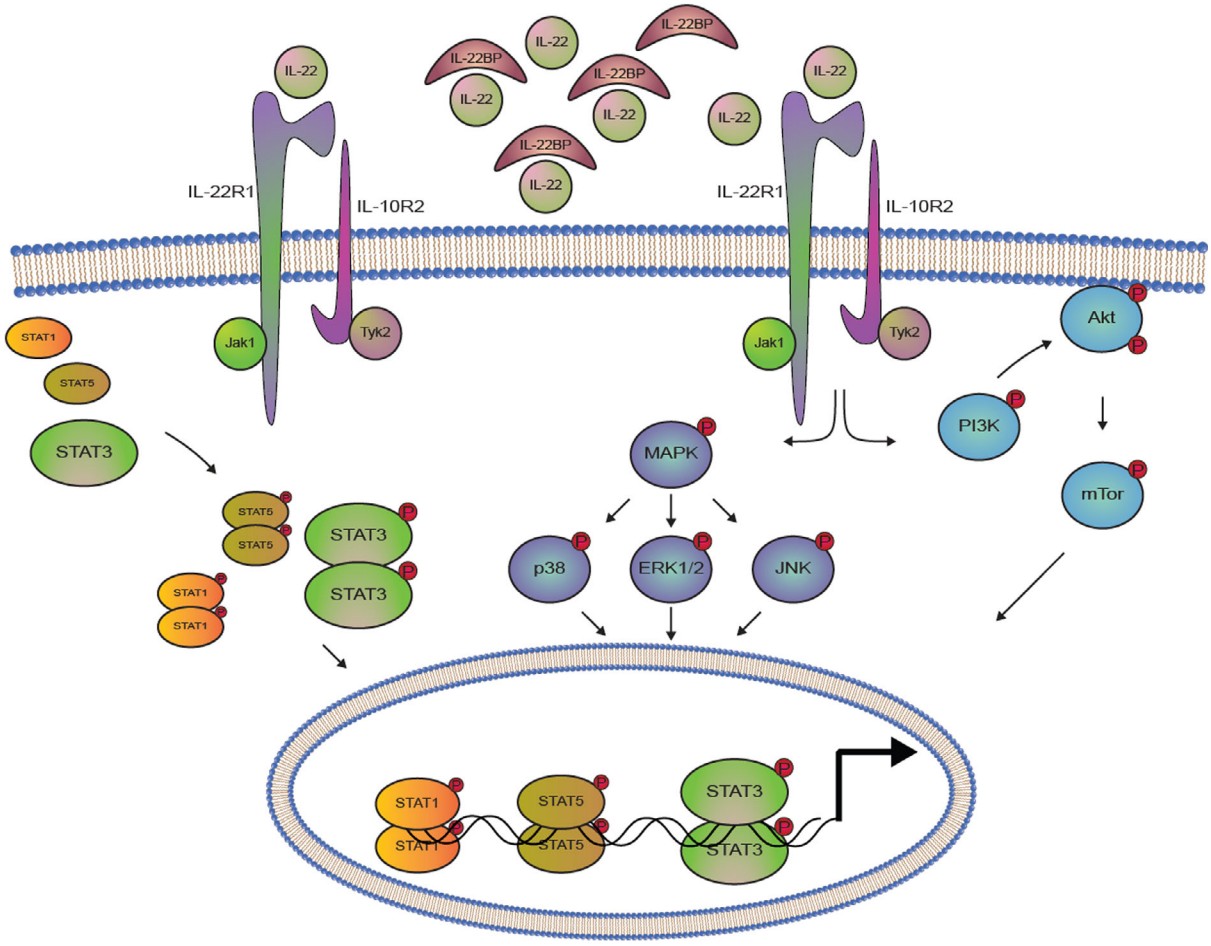

Fig. 2. IL-22R and its intracellular signalling. The heterodimeric IL-22R consists of the IL-22R1 and the IL-10R2. When IL-22 is not sequestered by the soluble protein, IL-22BP, it is able to bind the IL-22 receptor. Upon this binding, intracellular signalling is initiated, which starts with the activation of the receptor-associated JAKs and TYKs. Activation of these kinases mediates the phosphorylation of various STAT molecules, with STAT3 phosphorylation being the most pronounced. This phosphorylation allows STAT3 to form homodimers, which can translocate to the nucleus and regulate the transcription of STAT3-responsive genes. Furthermore, STAT1 and STAT5 molecules are also activated. IL-22R signalling is also seen to activate the MAPK pathways involving ERK1/2, JNK and p38, as well as the PI3K-Akt-mTOR pathway. Akt, protein kinase B; ERK, extracellular signal-regulated kinase; IL-10R, IL-10 receptor; IL-22BP, IL-22-binding protein; IL-22R, IL-22 receptor; JAK, Janus kinases; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; p38, p38 mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; STAT, signal transducer of activated T cells; TYK, tyrosine kinases.

several leukocyte-attracting chemokines such as chemokine (C-X-C motif) ligand (CXCL) 1, CXCL2, CXCL5 and CXCL8 that contributes to the recruitment of leukocytes to the sites of infection [40].

In summary, IL-22 is a cytokine that plays an essential role in skin homeostasis, wound healing and inflammation. In line with this, dysregulation of IL-22 and IL-22-producing immune cells is associated with several inflammatory skin disorders including psoriasis, atopic dermatitis (AD) and allergic contact dermatitis (ACD).

IL-22 IN SKIN DISEASES

Psoriasis

Psoriasis is an inflammatory skin disease that affects approximately 2% of the Caucasian population with clinical symptoms such as red, itchy, dry, rough and scaly skin. Signature histological features of psoriatic skin include thickening of the epidermis (acanthosis), hyperproliferation of keratinocytes (hyperkeratosis) and infiltration of immune cells in the dermis and epidermis [44]. Psoriasis is caused by a dysregulation of immune cells and cytokine

secretion in the skin [45]. Specifically, Th17 cell activation and IL-17 are believed to be the main drivers of the pathogenesis of the disease [44]. In addition, it has been reported that IL-22-producing cells and dysregulated IL-22 levels are involved in the pathogenesis of psoriasis [39]. Thus, elevated IL-22 expression levels in the skin and peripheral blood from patients suffering from psoriasis compared with healthy subjects have been observed [39]. Furthermore, specific genetic variants of IL-22 lead to altered skin barrier functions and this has been associated with the early onset of psoriasis and correlated with disease severity [46]. In addition to this, an impaired production of IL-22BP has been linked to the aggravation of skin inflammation in patients suffering from psoriasis [35]. These observations strongly indicate that IL-22 takes part in the pathogenesis of psoriasis in humans. This is supported by numerous studies that have demonstrated a central role of IL-22 in different mouse models of psoriasis [30,40,47,48].

Atopic dermatitis

AD is a heterogeneous inflammatory disorder of the skin that affects approximately 3% of the population worldwide. AD signature symptoms include dry, itchy skin with red to brownish-grey patches [49]. Immunologically, AD is characterized by the dominance of skin-homing Th2 cells that produce IL-4 and IL-13. These Th2 cells are believed to drive the onset and pathogenesis of the disease. Additionally, high levels of IL-22 are found in skin and blood of patients suffering from acute and chronic moderate-to-severe AD [50]. The elevated IL-22 concentrations are correlated with epidermal hyperplasia, acanthosis and skin barrier defects [50]. In patients suffering from AD, IL-22-producing T cells have been identified as the major sources of IL-22, and even higher frequencies of IL-22-producing T cells are found in patients suffering from severe AD than in patients suffering from psoriasis [49,51]. Therefore, given the pathogenic role of IL-22 in the development of AD, neutralizing-IL-22 treatments are being studied. The first double-blinded clinical trial using IL-22 blocking monoclonal antibodies (fezakinumab) improved the clinical symptoms in adults suffering from severe, chronic AD [52]. Subsequently, another study explored the molecular effects of fezakinumab in the skin from these patients compared with placebo. An improvement of epidermal inflammation and molecular skin changes were most robustly observed in patients that had high IL-22 background levels. This underscores that patients suffering from AD could advantageously be stratified towards different and more precise medical treatment options [53].

Allergic contact dermatitis

ACD is a common inflammatory T cell-mediated skin disease affecting about 10% of the adult population [54]. ACD can be highly disabling, and it is characterized by an intensely itching erythema, oedema and often vesicles at sites where the allergens contact the skin [54]. High IL-22 serum levels have been observed in patients suffering from ACD to nickel [55], and a considerable infiltration of IL-22-secreting T cells is found in the skin after re-exposure to nickel [56,57]. Likewise, the expression of IL-20 subfamily cytokines, including IL-19, -20, -22 and 24, is increased in affected skin from para-phenylenediamine (PPD) allergic patients compared with unaffected skin [58]. Interestingly, studies in mice did not support the implication of IL-22 but rather IL-24 in PPD-induced ACD [58]. In contrast, other studies in mice supported a pathogenic role of IL-22 in ACD. Thus, the inflammatory response in oxazolone-induced ACD was increased in mice lacking the IL-22BP [59] and prostaglandin E2 promoted oxazolone-induced ACD by facilitating IL-22 production from T cells [60]. These studies suggest that IL-22 can be involved in the pathogenesis of ACD; however, further studies are required to establish the exact role of IL-22 in ACD in humans.

FINAL REMARKS

IL-22 is a cytokine that mediates communication between the immune system and tissue barriers, and it plays a central role in skin homeostasis and inflammation but also in the pathogenesis of various skin disorders. Thus, increased IL-22 levels have been found and linked to several inflammatory skin diseases including psoriasis, AD and ACD. Blocking of IL-22 is being considered and studied as potential therapy for these diseases. However, the exact mechanisms behind the regulation of IL-22 and the exact role of IL-22 in the onset and development of psoriasis, AD and ACD remain to be determined. Increased knowledge on the regulation and function of IL-22 will provide a better basis for the development of potential IL-22 therapies against inflammatory skin diseases.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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