Review article

IL-25 (IL-17E) in epithelial immunology and pathophysiology

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IL-25, also known as IL-17E, is a unique cytokine of the IL-17 family. Indeed, IL-25 exclusively was shown to strongly induce expression of the cytokines associated with type 2 immunity. Although produced by several types of immune cells, such as T cells, dendritic cells, or group 2 innate lymphoid cells, a vast amount of IL-25 derives from epithelial cells. The functions of IL-25 have been actively studied in the context of physiology and pathology of various organs including skin, airways and lungs, gastrointestinal tract, and thymus. Accumulating evidence suggests that IL-25 is a "barrier surface" cytokine whose expression depends on extrinsic environmental factors and when upregulated may lead to inflammatory disorders such as atopic dermatitis, psoriasis, or asthma. This review summarizes the progress of the recent years regarding the effects of IL-25 on the regulation of immune response and the balance between its homeostatic and pathogenic role in various epithelia. We revisit IL-25's general and tissue-specific mechanisms of action, mediated signaling pathways, and transcription factors activated in immune and resident cells. Finally, we discuss perspectives of the IL-25–based therapies for inflammatory disorders and compare them with the mainstream ones that target IL-17A. (J Allergy Clin Immunol 2021;■■■:■■■-■■■.)

Key words: *IL-25, IL-17E, keratinocytes, epithelial cells, tuft cells, atopic dermatitis, psoriasis, contact dermatitis, inflammatory bowel disease, ulcerative colitis, Crohn disease, chronic rhinosinusitis, asthma, idiopathic pulmonary fibrosis*

Abbreviations used

AD:	Atopic dermatitis
BATF:	Basic leucine zipper transcription factor, ATF-like
CRS:	Chronic rhinosinusitis
DAZAP2:	Deleted in azoospermia DAZ-associated protein 2
DC:	Dendritic cell
IBD:	Inflammatory bowel disease
ILC2:	Group 2 innate lymphoid cell
iNKT:	Invariant natural killer T
JAK:	Janus kinase
MAPK:	Mitogen-activated protein kinase
NF-kB:	Nuclear factor kappa B
Pou2f3:	Pou domain class 2, transcription factor 3
SCC:	Solitary chemosensory cell
STAT:	Signal transducer and activator of transcription
TLR:	Toll-like receptor
TRAF:	TNF-receptor–associated factor
TRPM5:	Transient receptor potential cation channel
TSLP:	Thymic stromal lymphopoietin

Epithelia at mucosal and cutaneous surfaces form the protective barriers against various assaults from the external environment. It is now clear that except for mechanical protection, epithelia evolved as complex tissues that play an important role in sensing and integrating environmental cues.[1] Emerging evidence points to IL-25 (also known as IL-17E) as an intriguing "barrier cytokine" that participates in maintaining homeostasis, tissue adaption to external damages, alarming the immune cells, and stimulating the repair in case of injury.

First identified in 2001, IL-25 maps to chromosome 14q11 and belongs to the IL-17 family of cytokines (comprising 6 members: IL-17A, IL-17B, IL-17C, IL-17D, IL-25, and IL-17F). Nevertheless, it shares only 16% homology with IL-17A and has biological effects that largely differ from those of the other members of the family.[2-4] IL-17A is expressed by T_H17 cells, whereas IL-25 was originally described by Fort et al[2] as a T_H2-produced cytokine implicated in the induction of T_H2-like responses.[2] Indeed, infusion of mice with IL-25 induces the expression of cytokines such as IL-4, IL-5, and IL-13, and leads to increase serum IgE levels, blood eosinophilia, and pathological changes in the lungs and digestive tract characterized by increased mucus production and epithelial cell hyperplasia.[2]

In addition to T_H2 cells, IL-25 was later shown to be produced by various immune cells such as $CD8^+$ T cells, mast cells, macrophages, dendritic cells (DCs), eosinophils, basophils, and group 2 innate lymphoid cells (ILC2s).[1,5-8] Of interest, IL-25 is also produced by epithelial and endothelial cells[9] and may function in paracrine and autocrine manner, acting on both immune and tissue resident cells. Specifically, the epithelium-derived IL-25 has been demonstrated to play major roles in homeostasis and

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This work was supported by the Swiss National Science Foundation, Switzerland (grant no. 310030_175470/1) and the Ernest Boninchi Foundation, Switzerland.

Disclosure of potential conflict of interest: W.-H. Boehncke has received honoraria as a speaker or advisor from Abbvie, Almiral, Celgene, Leo, Lilly, Novartis, Sanofi, and UCB. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 8, 2020; revised December 8, 2020; accepted for publication December 16, 2020.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2020.12.628

pathologies of various organs. The IL-25 receptor–expressing cells are found in most organs including skin, kidney, pancreas, liver, brain, and intestine.[10] Cellular targets of IL-25 include T cells, ILC2s, specific myeloid populations, and invariant natural killer T (iNKT) cells, as well as nonhematopoietic-cell populations such as fibroblasts, epithelial cells, endothelial cells, and mesenchymal cells.[2,6,7,11-18] In nonimmune cells, IL-25 can stimulate cell proliferation,[19-21] inhibition of apoptosis,[22] production of inflammatory cytokines and chemokines,[20,23,24] modulation of cell-cell adhesion,[25,26] and cell motility.[21]

In this review, we summarize the current knowledge regarding the principles of IL-25 signaling. Subsequently, we provide an overview of the regulation and functions of IL-25 in the physiology and pathology of skin, gut, and airway epithelia. Next, we give an overview of the recent discoveries regarding IL-25 in the thymus. Finally, the perspectives of the use of IL-25 as a therapeutic target are discussed.

IL-25–INDUCED SIGNALING PATHWAYS

IL-25, as other IL-17 family members, is secreted from the cell in the form of disulphide-linked dimers. The binding receptor for IL-25, IL-17RB, requires association with IL-17RA to form a complex to mediate downstream signaling cascades in the target cells.[7] *In vitro*, IL-17RA binds to the IL-17RB-IL-25 complex rather than directly to IL-25.[27] Both receptor subunits are, however, required for an efficient signaling, because mice deficient for IL17RA or IL-17RB fail to respond to IL-25.[16,23,24,28] Besides forming the IL-25 receptor complex when paired to IL-17RB, the IL-17RA subunit is shared by the receptors of several IL-17 family cytokines: IL-17A and IL-17F (when paired to IL-17RC) and IL-17C (when paired to IL-17RE).[28,29] It was suggested that IL-25 may act as an IL-17A receptor antagonist,[30] although IL-17A has been reported to have no effect on the IL-17RB/IL-17RA complex.[31] However, IL-17RB can bind another IL-17 family member, IL-17B, although with a lower affinity.[3,9,32] In line with this, IL-17B and IL-25 were found to act as antagonists in mouse models of acute colonic inflammation, *Citrobacter rodentium* infection, and allergic asthma.[31]

IL-25 has been shown to activate several downstream signaling cascades, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) in a cell context–dependent manner (Fig 1).[8,33-37]

Upon binding to IL-25, the adaptor protein Act1 (activator of NF-kB-1, also known as CIKS) is recruited to the receptor to mediate multiple signaling pathways including immune response and cell fate decisions.[38-43] Act1 recognizes and ubiquitinates TNF-receptor–associated factor (TRAF) adaptors, which are also recruited to the receptor complex and are a key component in IL-17A and IL-25 signal transduction.[44]

Recruitment of TRAF6 is crucial for the IL-25R–mediated activation of the NF-kB pathway but is dispensable for the activation of MAPK.[34,42,45,46] Indeed, NF-kB activation can be blocked by a dominant-negative form of TRAF6. In addition, IL-25–stimulated expression of genes such as IL-6, TGF-β, and G-CSF was abolished in TRAF6-deficient cells.[34,47] Similarly, primary kidney epithelial cells from TRAF6-deficient mice showed a decrease in IL-25–induced Cxcl1 gene expression and loss of ligand-induced IκBα phosphorylation.[48]

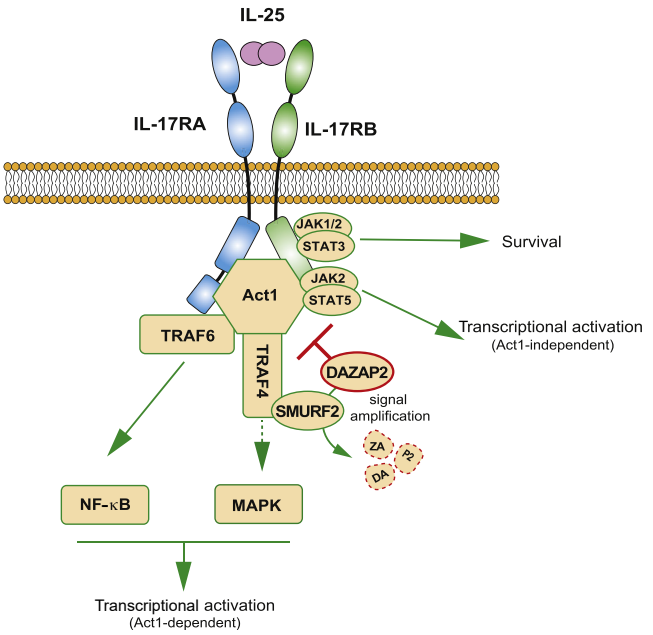

FIG 1. Pathways involved in the IL-25–mediated signaling. IL-25 binding to the receptor complex IL-17RA/IL-17RB induces the recruitment of Act1 and TRAF 4 and 6, SMURF2-dependent degradation of inhibitory protein DAZAP2, resulting in activation of NF-κB, MAPKs, and JAK/STAT pathways. *SMURF2*, Smadubiquitin regulatory factor 2.

TRAF4 also has been shown to mediate Act1-dependent signaling events downstream of IL-25 receptor.[48] TRAF4 activates the E3 ligase smadubiquitin regulatory factor 2, which leads to the ubiquitylation and subsequent degradation of the inhibitory protein DAZAP2 (deleted in azoospermia DAZ-associated protein 2),[48,49] resulting in the amplification of IL-25–mediated signaling. TRAF4 knockout mice exhibited blunted airway eosinophilia and reduced expression of T_H2 cytokines in response to IL-25 stimulation.[48] Of interest, primary T cells and epithelial cells derived from these mice showed abolished IL-25–induced phosphorylation of ERK1/2 and P38, revealing that activation of MAPKs might be somehow dependent on TRAF4. STAT5 is also recruited to the IL-25 receptor in a TRAF4-dependent and Act1-independent manner, via direct interaction with unique tyrosine residues Y444 and Y454 on IL-17RB.[41,50] Mechanistically, it was suggested that TRAF4-smadubiquitin regulatory factor 2–dependent degradation of DAZAP2 following the IL-25 stimulation facilitates the phosphorylation of Y444 and Y454 by JAK2, leading to the recruitment of STAT5 to the IL-17RB subunit. However, the exact molecular mechanism is yet to be discovered.[48] Conditional STAT5 deletion in T cells or epithelial cells led to a defective IL-25–initiated T_H2 polarization as well as defective IL-25 enhancement of T_H2 responses,[50] and ablation of the STAT5 or Act1 pathway resulted in the loss of IL-25 responsiveness.[35,40]

Instead, TRAF2, TRAF3, and TRAF5 seem to be dispensable for the IL-25 responses, even though they are involved in IL-17A–mediated signaling.[8,29,34,48,51]

IL-25 has been shown to activate the Act1-JAK1/2-STAT3 pathway, resulting in keratinocyte proliferation and the production of inflammatory cytokines and chemokines in murine skin.[20] Furthermore, IL-25–dependent STAT3 and NF-kB activation was required to maintain self-renewal of human cancer stem cells.[37]

In addition, IL-25 has been shown to potentiate expression of nuclear factor of activated T cells c1 and JunB transcription factors to upregulate the production of initial IL-4 and GATA-3 in early events of T_H2 differentiation.[6] Another transcription factor from the AP-1 superfamily, BATF (basic leucine zipper transcription factor, activating transcription factor–like), can cooperate with nuclear factor of activated T cells and has been recently identified as a modulator of ILC2 cell fate downstream of IL-25.[52,53] Moreover, BATF has been found to induce T_H9 phenotype by binding to the IL-9 gene promoter cooperatively with IRF4,[54-56] but the exact role for BATF in IL-25–induced production of IL-9 remains to be identified.

Although IL-25 shares some signaling events (such as recruitment of Act1) with the family counterpart IL-17A, the distinct physiological responses induced by the 2 cytokines *in vivo* reflect the existence of peculiar signaling differences.[39-43,57] Such distinct signaling outcomes may stem from the involvement of specific TRAF proteins or different usage of the same signaling molecules. This is the case of TRAF4, which was found to play "opposite" roles in IL-17A– and IL-25–mediated signaling. Under the IL-17A pathway, TRAF4 competes with TRAF6 for TRAF-binding domains on ACT1, thereby blocking TRAF6 and the subsequent activation of NF-kB–dependent genes.[58] This does not seem to apply to the IL-25 pathway.

IL-25 in the skin

IL-25 is constantly produced by keratinocytes in steady-state conditions. Although its transcripts are uniformly present across the epidermis, the protein is mostly accumulated within the granular layer.[21,59,60] It has been previously reported that bronchial, lung, and intestinal epithelia upregulate the production of IL-25 in response to various stimuli including allergens, fungal antigens, and Toll-like receptor ligands.[6,61-63] However, all the potential stimuli and precise mechanisms regulating the expression of IL-25 in the epidermis have not yet been identified.

IL-25 can act in an autocrine manner because normal keratinocytes express both subunits of the IL-25 receptor, IL-17RA and IL-17RB.[20,21] Moreover, IL-25 stimulation of cultured murine keratinocytes induced the expression of both IL-17RB and IL-25, suggesting an autocrine self-regulation of IL-25.[20] IL-17RB transcript and protein levels have been found to increase along with calcium-dependent human keratinocyte differentiation[21]; therefore, the terminally differentiated keratinocytes from the upper layers might have a higher sensitivity to IL-25 stimulation. The constant production and accumulation of IL-25 suggests its homeostatic role; however, the functions of IL-25 in the epidermis still remain obscure (Fig 2, *A*).

IL-25 has been shown to promote proliferation of primary murine keratinocytes, enhance the expression of Ki67 proliferation marker and cell cycle progression genes Ccl2 and Fn1, and increase the number of cells in S and G2/M phase of the cell cycle.[20] In our recent study, IL-25 strongly increased metabolic activity and proliferation of cultured primary human keratinocytes. Moreover, IL-25 stimulated keratinocyte proliferation in the reconstituted human epidermis model but it did not cause acanthosis.[21]

The balance between keratinocyte proliferation and differentiation is crucial to maintain epidermal homeostasis. IL-25 was found to decrease the filaggrin mRNA levels in differentiating keratinocytes exposed to a high concentration of calcium in some studies[59,64] but not in the others.[21] Moreover, IL-25 may inhibit differentiation of keratinocytes indirectly by promoting production of IL-4 and IL-13, which exhibit a downregulatory effect on loricrin and involucrin expression crucial for skin barrier integrity.[65] Surprisingly, IL-25 rather favored the terminal differentiation in primary human keratinocytes cultured in low calcium, which reflects more the environmental conditions of the basal layer of human epidermis.[21] Future studies should clarify the involvement of IL-25 in the terminal differentiation of keratinocytes.

The production of antimicrobial peptides by keratinocytes is the first line of host defense against infection. Interestingly, *in vivo* studies showed that IL-25, unlike IL-17A,[66-69] does not seem to be involved in antimicrobial defense because the host resistance to pathogens was not impaired in the mice deficient for IL-25 in the epidermis compared with the wild type.[20] In addition, IL-25 did not affect transcription of β-defensin 2, LL-37, and S100A7 in cultured human primary keratinocytes and showed no synergy with IL-17A.[21,64]

Following skin injury, basal keratinocytes at the edges of the wound actively proliferate, migrate, and subsequently differentiate to repair the damage and restore the epidermal homeostasis.[70,71] Although accumulating evidence suggests that IL-17A contributes to skin healing,[72,73] in cultured human primary keratinocytes IL-17A exhibits moderate proproliferative effects, globally inhibits terminal differentiation, and does not stimulate cell migration.[21] In this regard, it is interesting to note that IL-25 is capable of promoting not only proliferation and differentiation but also migration, increasing both cell speed and displacement of keratinocytes *in vitro*.[21] Surprisingly, IL-25 seems to be even more potent in enhancing keratinocyte migration than IL-22, which is known to stimulate prohealing functions.[69,74] Furthermore, IL-25 was found to stimulate the expression of keratins 6, 16, and 17 at the mRNA level. Although barely present in the healthy skin, these "stress-inducible" keratins are rapidly upregulated after injury or in various hyperproliferative disorders, such as psoriasis.[38,75] Nevertheless, further studies are needed to explore the role of IL-25 in skin regeneration and repair *in vivo*.

Although initially thought to be exclusively involved in T_H2 responses in epithelial tissues,[5-7,19,36,76,77] IL-25 was recently found to be upregulated in the lesional tissue in several skin inflammatory disorders: atopic dermatitis (AD),[59,78,79] psoriasis,[20,60,64] and contact dermatitis.[80] The fact that IL-25 is implicated in the pathogenesis of skin diseases of very different etiology suggests that its role in pathology may be much broader than previously thought, although the precise functions of IL-25 in the context of skin inflammation remain unclear.

AD is the most common chronic inflammatory skin disease characterized by type 2–driven inflammation and skin barrier dysfunction often associated with filaggrin mutations.[81,82] Keratinocyte-derived IL-25 emerges as an important factor in acute and chronic allergic skin inflammation,[79] and it was found to be overexpressed in the epidermis of patients with AD and in murine AD models.[12,59,64,78,83,84] The expression of IL-25 in human keratinocytes, along with Toll-like receptor (TLR)1, TLR6, and IL-33, can be also upregulated by antigens such as house dust mites.[85] Moreover, TLR1/6-mediated activation of TRAF6, IL-1 receptor–associated kinase 1, TGF-β–activated kinase 1, and NF-kB pathways can induce the production of IL-25 and IL-33 by keratinocytes.[85] Hvid et al[59] showed that IL-25 downregulates filaggrin synthesis in cultured human keratinocytes and may

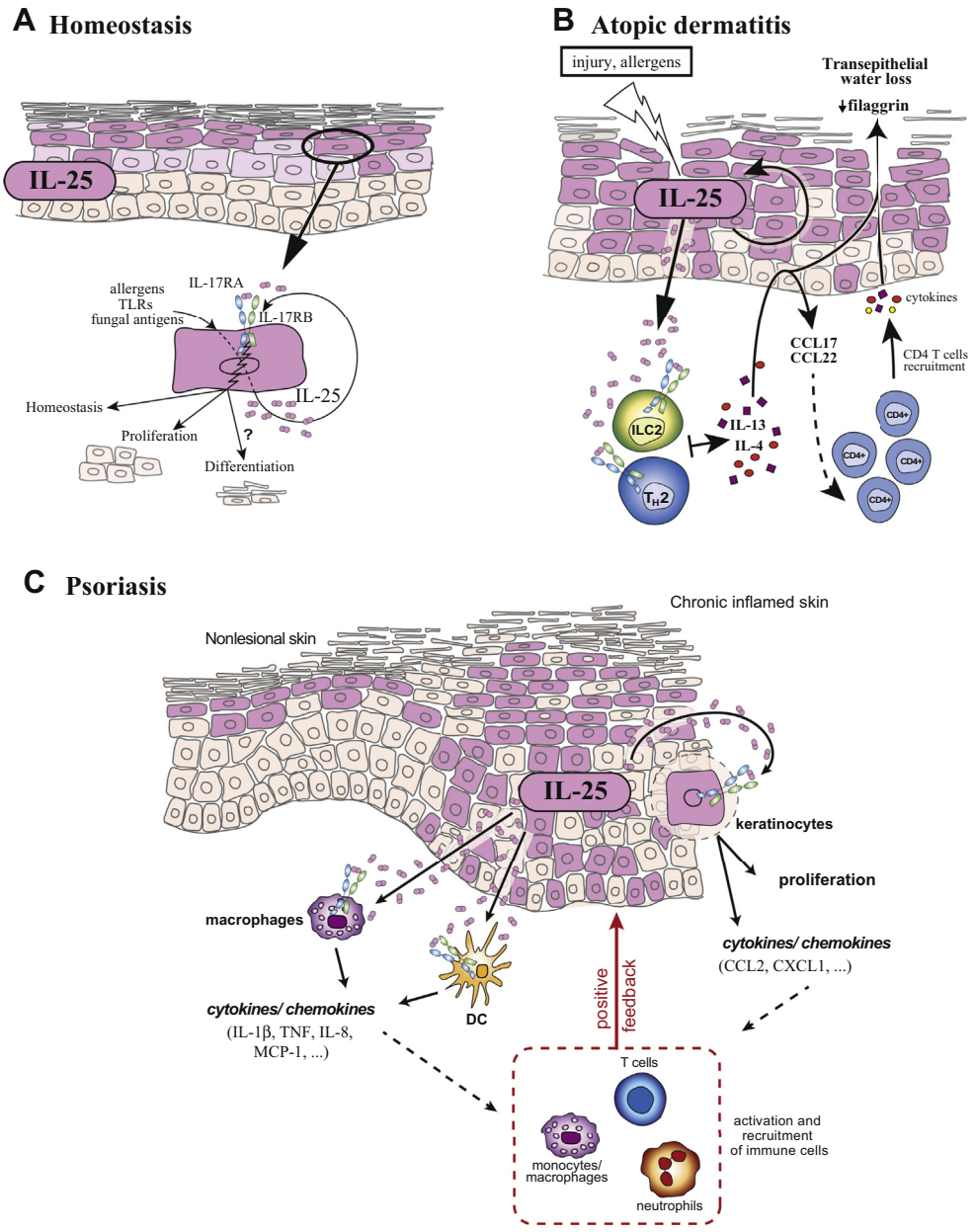

FIG 2. The role of IL-25 in the epidermal homeostasis, and in the pathology of AD and psoriasis. **A,** In steady-state conditions, IL-25 is produced at low amount in the granular layer of the epidermis. Various stimuli may trigger the release of IL-25 from keratinocytes, which can act in an autocrine manner to maintain tissue homeostasis. IL-25–producing cells are marked in purple. **B,** Stimuli provoking AD cause an overproduction of IL-25, which can act on both keratinocytes and immune cells, inducing amplification of type 2 response, keratinocyte proliferation, and disruption of the epidermal barrier function. **C,** In psoriasis, IL-25 is overexpressed in all layers of lesional epidermis and is linked to epidermal acantosis and dermal infiltration by immune cells.

thereby provide a link between skin inflammation and the loss of skin barrier function in AD. Moreover, IL-25 was found to be implicated in the pathophysiology of itch by significantly increasing the expression of a well-known pruritogen endothelin 1 in keratinocytes via the ERK1/2 and JNK pathways.[78]

Alarmins IL-25 and IL-33 were identified as predominant ILC2-inducing cytokines in response to skin allergen challenge, with thymic stromal lymphopoietin (TSLP) having a less marked role.[84] Ovalbumin-sensitized skin from mice deficient for IL-25 in epidermis demonstrated reduction of epidermal thickening, $CD4^+$ T-cell infiltration, and expression of IL-13, Ccl17, and Ccl22 mRNA compared with controls.[79] Recent data suggest that IL-25 acts directly on ILC2s to induce IL-13, which in turn acts back on keratinocytes to promote their proliferation and production of T-cell–attracting chemokines.[79] A similar crosstalk between epithelial cells and ILC2s has been demonstrated during helminth infection in the small intestine of mice.[86-88] Altogether, IL-25 mediates the recruitment of type 2 cytokine–producing

ILC2s and thus may play a dual role in promoting AD both by stimulation of type 2 responses and through direct action on keratinocytes (Fig 2, *B*).[84]

Data from *in vitro* and clinical studies indicate that IL-17A is a critical effector cytokine in psoriasis.[89-91] IL-17A acts directly on keratinocytes to stimulate proliferation and reduce differentiation, upregulate production of proinflammatory cytokines and antimicrobial peptides, including psoriasis autoantigen LL37, and neutrophil-, macrophage-, as well as lymphocyte-attracting chemokines.[92-94] However, accumulating evidence indicates that IL-25 may be another member of the IL-17 family implicated in the pathogenesis of psoriasis. *In vitro* stimulation with IL-25 or IL-17A, but not IL-17C, IL-1, or TNF-α, induced robust IL-25 expression in primary murine keratinocytes, and IL-17A$^{-/-}$ mice showed reduced IL-25 expression in lesional skin in the imiquimod-induced psoriasis model.[20] Our recent findings showed that both IL-22 and IL-17A induced the production of IL-25 in the reconstituted human epidermis model, whereas IL-17A increased the surface expression of the IL-17RB receptor subunit.[21] Both IL-17A and IL-22 are overexpressed in psoriasis and might function as fine-tuners of the IL-25–related effects during the development of the disease. Importantly, IL-17A is not required for IL-25–induced skin inflammation, and experiments in IL-17A$^{-/-}$ mice revealed that IL-25 signaling in keratinocytes is independent of IL-17A.[20] Another inflammatory cytokine IL-36 has been shown to play a critical role in the psoriasis pathogenesis along with the IL-23/IL-17/IL-22 axis.[95,96] However, this is particularly true for generalized pustular psoriasis,[97] and putative interactions between the IL-36 signaling and the IL-25 expression require further investigation.

Studies using mouse models have shown that IL-25 is critical in the pathogenesis of psoriatic-like skin inflammation. Injection of recombinant IL-25 intradermally into ear or dorsal skin of mice induced psoriasis-like pathology, including epidermal acanthosis and dermal thickening, immune cell infiltration in the dermal layer, and pustule formation.[20,98] IL-25 appears to be a key factor required for the recruitment of innate immune cells because it increases the numbers of macrophages, neutrophils, and DCs in mouse lesional skin.[20,98] Indeed, IL-25 stimulation induced chemokines regulating inflammatory immune cells such as Ccl2 and Cx3cl1 in an Act1-dependent manner.[20] *In vitro* studies confirmed that human dermal macrophages actively uptake the keratinocyte-derived IL-25 in a receptor- and clathrin-dependent manner, which leads to the production of inflammatory cytokines and chemokines such as TNF-α, IL-6, CCL-2 (MCP-1), and IL-8.[60,98] Moreover, IL-25 was shown to upregulate the expression of proinflammatory cytokines IL-1β, IL-6, IL-8, TNF-α, CCL-5, and GM-CS by human fibroblasts *in vitro*.[99,100] Furthermore, IL-25 enhances keratinocyte proliferation by activating STAT3 and contributes to epidermal hyperplasia in imiquimod-induced psoriatic model.[20] Consistently, genetic deletion or IL-25 neutralization greatly ameliorated psoriasiform skin inflammation and reduced the formation of neutrophilic abscess-like structures induced by imiquimod application or tape stripping.[20,98] This corresponds well with the finding that Act1-mediated signaling downstream of IL-17 cytokines within keratinocytes is essential for the formation of neutrophilic pustules.[92]

In humans, IL-25 was found to be highly overexpressed in all layers of lesional psoriatic epidermis compared with nonlesional and healthy skin.[60] The fact that a single nucleotide polymorphism (rs79877597) in the *IL25* gene positively correlates with severe forms of the disease and the presence of psoriatic arthritis further supports its pathogenic role.[101] Improved symptoms after phototherapy were shown to be associated with a decrease in IL-25 serum levels in a patient presenting high steady-state levels of this cytokine.[102]

All these findings highlight the importance of IL-25 in shaping the pathogenic features in development of psoriatic skin inflammation through multiple mechanisms (Fig 2, *C*).

Finally, the increase in epidermal IL-25 expression is also observed in patients with contact dermatitis.[80] Unexpectedly, studies revealed that although IL-25 is not essential for either DC function or T_H2-cell differentiation in the sensitization phase, it induces local inflammation in the elicitation phase of FITC-induced contact hypersensitivity in mice.[80] Precisely, IL-25 produced by mast cells and keratinocytes stimulates dermal DCs to produce IL-1β and thereby contributes to T_H17 but not T_H2-cell activation. Indeed, IL-25 injections increase T_H17-related cytokines IL-1β, IL-6, and TNF in the skin.[80] Notably, many observations in mice suggest the involvement of IL-25 in induction of both T_H2 cytokine–associated eosinophilia and T_H17 cytokine–associated neutrophilia,[2,103-105] contradicting a common belief depicting IL-25 as the cytokine favoring exclusively type 2 responses. However, further studies are needed to clarify the precise role for IL-25 in various skin inflammatory diseases and the potential therapeutic applications.

IL-25 IN THE GASTROINTESTINAL TRACT

The IL-25 function in the gut is the best characterized in the context of host response to eukaryotic infection.[106] In 2016, specialized cells of chemosensory lineage—tuft cells—were identified as the main source of IL-25 in the intestinal mucosa that play a key role in the gastrointestinal homeostasis in mice.[86-88] Tuft cells express G protein–coupled olfactory receptors and act as luminal sensors detecting metabolic products secreted by parasites.[107-109] Under normal conditions, tuft cells are a rare cell type that constitutes about 0.5% of gut epithelial cells. However, they undergo a quick and transient hyperplasia as a part of the host immune response and the tuft cell–derived IL-25 is crucial for driving type 2 immunity in the murine intestine.[5]

Accumulating evidence suggests that tuft cells constitute a diffuse chemosensory system regulating local homeostasis in most epithelia of murine hollow organs.[110] Although they adapted to sensing different ligands depending on their microenvironment,[106,111-113] tuft cells from all the tissues constitutively express IL-25,[113] and it is feasible to suggest that tuft cells from different organs have, in principle, similar regulatory functions.

von Moltke et al[87] characterized a positive feedback mechanism where upon infection of mice with roundworm *Nippostrongylus brasiliensis* the elevated production of IL-25 by tuft cells recruited CD4$^+$ T cells and BATF-dependent ILC2s[53] to the lamina propria. The products of these cells, T_H2 cytokines IL-4 and IL-13, are critical for the antihelminth immunity.[114,115] They induce activation of IL-4 receptor–expressing progenitors in the intestinal epithelium, directing cell fate decisions toward tuft and goblet cell differentiation.[86,87,116] The resulting hyperplasia of mucus-producing goblet cells induces increased mucus secretion and expulsion of dwelling helminths.[117] At the same time, the tuft cell hyperplasia in the small intestine reinforces the host response, thus closing the positive loop (Fig 3).[118,119] The

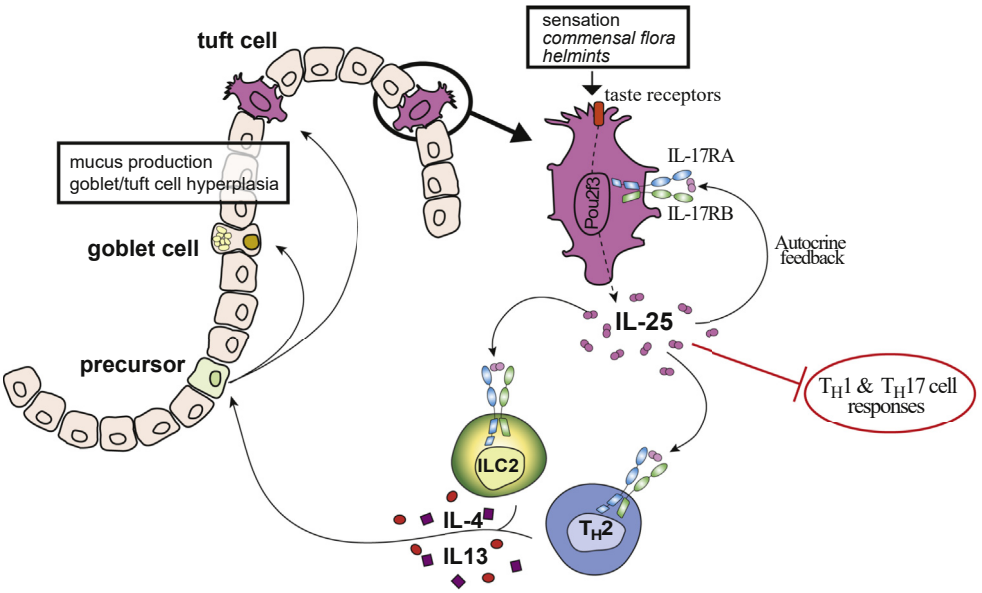

FIG 3. IL-25 in the gastrointestinal homeostasis. Tuft-cell–derived IL-25 mediates a positive feedback loop between epithelial and immune cells in the gut mucosa, leading to the amplification of T_H2 responses and promoting differentiation toward goblet and tuft cells in response to external cues (commensal flora, infections, etc).

increase in tuft cell frequency was found to be unaffected by the absence of TSLP or IL-33 signaling.[87] Knockout of IL-13 or STAT6 but not IL-4 in mice suppressed the upregulation of IL-25 in response to helminth infection.[120]

Therefore, IL-25 appears to be a key player in linking the chemosensation by tuft cells and type 2 immunity. Notably, tuft cells express IL-25 even in normal conditions[121] and the lack of homeostatic IL-25 in uninfected IL-25–knockout mice leads to further reduction of the tuft cell numbers.[87] The bulk IL-25 production in intestinal epithelium can be driven by commensal flora and is decreased in germ-free or antibiotic-treated wild-type mice, reflecting complex interrelationships between gut microbiota and the host immune system.[31,61,122]

It is still not clear how exactly the IL-25 production is upregulated to activate the tuft cell-ILC2 circuit. The work of Howitt et al[88] demonstrated that the signal transduction in the tuft cells in response to intestinal colonization with *Tritrichomonas muris* is dependent on the taste-specific G protein subunit gustducin-α, as well as TRPM5 (transient receptor potential cation channel, subfamily M, member 5). The gustducin-null or TRPM5-null mice showed defects in ILC2 recruitment, IL-13 production, and tuft cell and goblet cell hyperplasia.[88] Thus, the expression and/or regulated secretion of IL-25 and possibly other alarmins is likely initiated downstream of the TRPM5 signaling cascade. Furthermore, Reynolds et al[31] reported an induction of IL-25 mRNA expression in cultured murine colon epithelial cells through TLR4 (agonist LPS), TLR1 and 2 (agonist Pam3CSK4), and muramyl dipeptide (MDP/NOD2) pathways.

The specification of tuft cell lineage depends on Pou2f3 (Pou domain class 2, transcription factor 3), and Pou2f3-deficient mice contain no tuft cells and exhibit defects in IL-25 expression and mucosal type 2 responses to helminth infection.[86] However, it is not known whether there is a functional link between the 2 proteins. Interestingly, Pou2f3 (also known as Oct-11, Epoc-1, or Skn-1) is highly expressed in epidermis,[123] which also produces IL-25 at steady state.

The transcriptome analysis of Trpm5-positive (which are mainly tuft) cells in mice revealed relative overexpression of not only IL-25 but also its receptor IL-17RB compared with other intestinal cell types,[124] and that expression of IL-17RB was further upregulated during nematode infection.[120] Therefore, it is feasible that the above-described positive feedback mechanisms are reinforced in an autocrine manner. However, the IL-25-IL-17RB signaling can be negatively regulated by the infectious agents to impair the host defense. For instance, IL-25 and IL-17RB were found to be downregulated by *Helicobacter pylori* protein cagA through the PI3K/AKT pathway in gastric mucosa of both patients and mice.[125] In the early phase of *H pylori* infection, the IL-25-IL-17RB pathway promotes the production of antibacterial protein regenerating islet-derived protein 3 (REG3a) and gastric epithelial cell–derived CXCL1/2/5/6 to attract $CD11b^+CD11c^-$ myeloid cells. Consequently, IL-17RB was suggested as a potential early intervening target in this disease.[125]

IL-25 has been reported to play both pathogenic and protective functions in different inflammatory bowel disease (IBD) settings, which is characterized by an imbalance of the T_H1/T_H2 cytokine response. Ulcerative colitis is a chronic IBD in which immune dysregulation is driven mostly by $IL\text{-}17RB^+$ natural killer T cells and nuocytes producing type 2 cytokines such as IL-5 and IL-13.[126-129] Neutralizing antibodies to IL-25 or IL-17RB improved pathology in mice with oxazolone-induced ulcerative colitis.[130,131] In agreement with this, Reynolds et al[31] demonstrated that epithelial-specific deletion of IL-25 decreased colonic inflammation and reduced expression of IL-1β, IL-6, TNF-α, and CCL2 in another murine model, dextran sulfate sodium–induced colitis. In yet another study, $IL\text{-}25^{-/-}$ mice were also significantly protected from both acute and chronic dextran sulfate sodium

challenge.[19] In contrast, McHenga et al[132] reported that the IL-25 injections in parallel with dextran sulfate sodium administration resulted in elevated levels of IL-23 and TGF-β1 (but not IL-17A) in colon tissues and decreased inflammation. IL-25 administration was able to protect mice from peptidoglycan-induced T_H1-driven colitis.[77] Using a model for colitis-induced colon cancer, Thelen et al[133] showed that IL-25 suppression by blocking antibody resulted in increased colitis scores but greater tumor burdens compared with isotype control–treated mice; however, IL-25 knockouts showed no difference in colonic tumor development compared with the wild type. Despite the massive data in mouse models, more studies are needed to clarify the functions of IL-25 in patients with ulcerative colitis.

Another type of IBD, Crohn disease, is often associated with an overproduction of IFN-γ, TNF-α, and other T_H1 and T_H17 cytokines.[126,134,135] Neither IL-25 nor IL17-RB was elevated in the gut tissue explants from patients with Crohn disease, and another study showed decreased levels of IL-25 (in contrast to IL-17A) in the mucosa of patients with both types of IBDs.[77] Moreover, IL-17A, but not IL-25, has been proposed to have a profibrotic role in Crohn disease.[136] Notably, alterations in the coding regions of the IL-25 gene have been reported not to play a significant role in IBDs.[137]

The anti-inflammatory activity of IL-25 is likely conveyed through inhibiting T_H17 and T_H1 responses by the induction of IL-13 in DCs and inhibition of IL-23 production by macrophages and IL-12 by mucosal $CD14^+$ monocyte-like cells.[77,120,134,138] A decrease in commensal-dependent expression of IL-25 in intestinal epithelium correlates with elevated IL-23 and increased presence of T_H17 cells in the large intestine of mice.[61] $IL\text{-}25^{-/-}$ mice chronically infected with worm *Trichuris muris* developed severe intestinal inflammation associated with elevated IFN-γ and IL-17A and recovered the infection-induced expression of IL-4, IL-5, and IL-13 when type 1 cytokines were blocked.[5] In line with this, IL-25 also has been found to regulate autoimmune processes promoted by T_H17 cells.[138-141]

IL-25 IN THE AIRWAYS

The sources of IL-25 in the airways include T_H2 cells, alveolar macrophages, mast cells, activated eosinophils and basophils, and airway endothelial and epithelial cells.[7,13,142,143] In the past years, the airway epithelial cells emerged as critical players in regulation of innate and adaptive immunity at the mucosa site, in particular, via secretion of IL-25 and other proinflammatory cytokines such as TSLP and IL-33.[144]

Similarly to the gut epithelium, IL-25–expressing tuft cells have been identified in the murine trachea, whereas other cell types (basal, ciliated, club, goblet, ionocyte, and neuroendocrine cells) did not express IL-25.[145] Kohanski et al[146] described a cell lineage named solitary chemosensory cells (SCCs) as a primary source of IL-25 in the human sinonasal epithelium,[147] which possibly represent the airway tuft cells.[113,147] Analogously to the chemosensory machinery of the gastrointestinal epithelia, the activation of taste receptors in the nasal SCCs regulates the immune response to infections and allergens.[113] SCCs occur throughout the entire respiratory tract; however, their presence in distal intrapulmonary airways and alveoli is species restricted.[148] A positive IL-25–mediated tuft cell-ILC2 circuit likely exists in the human nasal cavity[149] and in the airways of mice.[150,151]

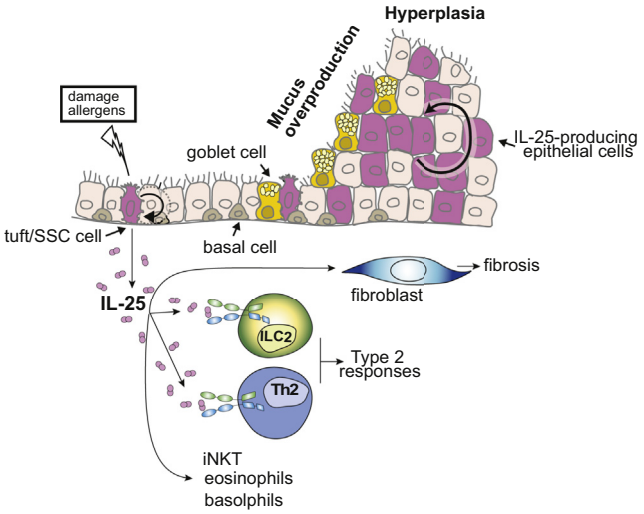

FIG 4. The function of IL-25 in the airways. IL-25 produced by epithelial tuft cells (and possibly other cells) in response to damage and allergens induces tissue infiltration by immune cells and type 2 responses, epithelial hyperplasia, and fibrosis in the airways.

Other studies reported that *in vitro* IL-25 is constitutively produced by normal human bronchial epithelial cells[62] and by most bronchial epithelial cells in the mucosa of atopic subjects with asthma,[14,152] and that its expression can be induced by cytokine, allergen, or double-stranded RNA stimulation in human nasal epithelial cells,[153] murine lung epithelial cells,[154] or alveolar epithelial cells.[6]

Numerous studies reported an upregulation of both IL-25 and IL-17RB in the airway epithelia and submucosa and in the lung tissue upon allergen provocation in mice and humans.[6,14,62,76,153,155-159] The airborne allergens (such as house dust mite) and their proteases cause a rapid release of prestored IL-25 (possibly by an active secretory mechanism) and an increase in transcription of IL-25 mRNA.[62] The house dust mite–induced IL-25, IL-33, and TSLP expression was found to be dependent on the intelectin-EGFR-ERK pathway in human airway epithelial cells and in murine asthma models,[160] and the optimal production of IL-25 from bronchial epithelial cells was found to depend on proteolytic enzyme MMP7.[161]

Indeed, IL-25 levels have been found to be elevated in multiple respiratory conditions. Even though IL-25 has a rather protective role in case of infectious diseases, for example, Aspergillus[103] or viral infections,[162,163] the associated upregulation of T_H2 pathways may provoke pathologies such as chronic rhinosinusitis (CRS) and asthma (Fig 4).[164]

CRS is one of the most common diseases in the upper respiratory tract, and can be subdivided into CRS with or without nasal polyps. CRS without nasal polyps is usually characterized by T_H2 response and tissue eosinophilia, in contrast to CRS with nasal polyps, which predominantly shows T_H1 response. The levels of IL-25 and ILC2 numbers are elevated in the nasal polyps,[165,166] and patients with CRS without nasal polyps show increased numbers of clustered SCCs in nasal polyp tissue, which is significantly greater than the increase in tuft cells upon the helminth gut infection in the mouse model.[146]

Asthma bronchiale is a heterogeneous disease characterized by physiological and structural changes in the airways, mucus hyperproduction, and airway hyperresponsiveness.[7] T_H2-biased

inflammation was observed only in half the patients with asthma[167,168]; however, IL-25–high pattern appears to be associated with poorly controlled disease.[169]

In animal models, IL-25 can initiate allergic asthma–like inflammation in the airways by selective amplification of T_H2 pathways, resulting in overproduction of IL-4, IL-5, IL-13, and eotaxin, recruitment of eosinophils and $CD4^+$ T cells, mucus hypersecretion, airway hyperreactivity, and IgE and IgG production.[2,6,12,76,103,159,170] Airway epithelium–derived IL-25 has a potential to activate DCs.[12,40,171,172]

Inhibition or deficiency of IL-25 reduces the associated T_H2 inflammation in allergen-induced asthma models,[6,76,159,173,174] and IL-17RB–deficient mice fail to develop a robust T_H2 cytokine response.[157,159] Furthermore, the signaling molecules Act1, STAT5, STAT6, and TRAF4 in the airway epithelium and in $CD4^+$ T cells have been shown to be critical factors in the IL-25–induced allergic airway inflammation.[35,48,175]

In the airway epithelium itself, IL-25 induces proallergic chemokine production, an increase in goblet cells and in mucus secretion (similar to the gastrointestinal epithelium), overall epithelial cell hyperplasia, and airway hyperreactivity.[6,103] IL-25 was found to modulate epithelial-mesenchymal transition of alveolar epithelial cells,[176] which may contribute to disrupted epithelial barrier function in asthma.[177,178]

An increasing evidence suggests a critical role for IL-25 in the epithelial-mesenchymal crosstalk and local tissue remodeling,[176] which can lead to tissue fibrosis when dysregulated. Fibrosis accompanies numerous pulmonary diseases, including acute respiratory distress syndrome, asthma, bacterial infection, bronchiolitis, emphysema, lung cancer, pneumonia, idiopathic pulmonary fibrosis, and sarcoidosis, with type 2 cytokines being elevated in many of these conditions.[129] The ability of IL-25 to drive lung fibrosis has been demonstrated in mouse models.[150,170,176] Moreover, IL-25, its receptor IL-17RB, and ILC2s are upregulated in both alveolar epithelial cells and lung fibroblasts of patients with idiopathic pulmonary fibrosis.[150,176] IL-25 can directly activate fibroblasts by inducing their differentiation into myofibroblasts, proinflammatory cytokine production, migration, proliferation, and increased extracellular matrix (collagen I/III and fibronectin) deposition in nasal polyps and in lungs.[174,176,179,180] Moreover, IL-25 can influence tissue remodeling indirectly through IL-13, which is strongly linked to pathology-associated fibrosis.[129] In addition, $CD31^+$ endothelial cells express IL-17RB, and the recruitment of endothelial progenitor cells to the lung and subsequent neovascularization following allergen exposure is also dependent on IL-25.[7,170,174]

The abundance of IL-25 receptor expression across multiple immune and structural cell types in the tissue may explain the profound effects of IL-25 in the initiation and progression of allergic inflammation. An increasing evidence points out that IL-25 is involved in numerous feedback and feed forward loops in interactions between multiple cytokines and cell types. Epithelial-derived IL-25 can function in an autocrine manner to sustain IL-17RB expression, and induce the epithelium to produce more IL-25 and other potent innate cytokines, such as IL-33 and TSLP, thus intensifying the allergic airway inflammation.[6,158,174] IL-25 and IL-4 pathways have been shown to reinforce each other to induce type 2 inflammation in different cell types (in human lung tissue culture, primary alveolar macrophages, and the THP-1 monocytic cell line).[1,6,158,181,182] However, the other T-cell–related cytokines IL-17A, IL-17F, and IL-22, which are also upregulated in allergic respiratory conditions and linked to their pathology,[18,183,184] may counterbalance the effects of IL-25. An opposing role for IL-17A and IL-25 has been reported for TSLP production in human nasal epithelial cells[154] and for IL-17B and IL-25 during airway inflammation in murine model.[31] In contrast to studies on epidermis,[21] IL-22 was shown to inhibit IL-25 production in lung epithelial cells.[185]

IL-25 IN THE THYMUS

One of the 4 recently identified subsets of medullary thymic epithelial cells in mice was found to share molecular characteristics of the chemosensory tuft cells, such as expression of Dclk1, Sox9, Trpm5, and Pou2f3.[186,187] The peculiarity of this subset is the high and exclusive production of IL-25 in the thymic stroma. However, the role of the thymic tuft cells remains uncertain.[113]

It is worth underlining that several cell populations in the thymus express IL-17RB and thus may potentially respond to IL-25. This includes subsets of $CD3^+$ thymocytes, thymus-resident type 2 innate lymphoid cells (ILC2s, defined as $ILC^-TCR^-CD127^{hi}$Tbet-$ROR\gamma t^-GATA3^+$), and iNKT cells (ie, iNKT2 and iNKT17).[188,189]

Bornstein et al[186] found that specific ablation of the thymic tuft-cell population in *Pou2f3*$^{-/-}$ mice is accompanied by a specific increase in thymic ILC2 within the $CD45^+IL\text{-}25R^+$ population. In contrast, Miller et al[187] demonstrated that tuft-cell deficiency results in the decrease in IL-4 secreting intrathymic iNKT2 cells (defined as $TCR^{int}CD1d^+PLZF^+ROR\gamma t^-$). Trpm5$^{-/-}$ mice had a similar phenotype, which showed that the taste transduction pathway is required for the function of thymic tuft cells.

Moreover, thymic tuft cells were shown to express MHC class II molecules, which makes them potentially capable of presenting self-antigens not covered by other medullary thymic epithelial cell populations.[187] Indeed, athymic mice transplanted with Pou2f3$^{-/-}$ thymi (thus having peripheral but lacking thymic tuft cells) generated an IL-25–directed antibody response on immunization with IL-25, whereas wild-type mice were tolerant. Thus, thymic tuft cells seem to participate in enforcing tolerance to unique tuft-restricted antigens including IL-25. Of note, IL-25$^{-/-}$ mice exhibited no defects in lymphocyte development in the thymus.[5] Further efforts to better understand the role of thymic tuft cells and IL-25 in shaping type 2 populations and immune responses in the thymus are therefore warranted.

THERAPEUTIC PERSPECTIVES

Up to date, no clinical studies have been initiated using selective IL-25 blockade.[190] However, the potential for IL-25 blockade as a therapeutic approach to decrease symptoms associated with T_H2 inflammation has been recognized in various contexts, with encouraging data emerging from *in vivo* studies.[191,192] In animal models of asthma, overexpression or administration of recombinant IL-25 triggers allergic responses characterized by T_H2 cytokine expression, eosinophilia, and mucus hypersecretion.[6,159,193] Administration of anti–IL-25 antibodies has been shown to significantly reduce airway hyperreactivity, levels of T_H2-associated cytokines, IgE levels, and goblet cell hyperplasia.[2,24,76] Moreover, IL-25 knockout mice displayed reduced lung pathology in an asthma model.[76] These data indicate that the effects of blocking IL-25 may be due to both reduction of T_H2 cytokines in allergic responses and inhibition of expression

of critical chemokines that promote an exacerbated inflammatory response.[157] Apart from association with asthma, the therapeutic effects were reported in a Staphylococcal enterotoxin B–induced murine nasal polyps' model where blocking of IL-25 reduced levels of local inflammatory cytokines and nasal polyp formation capacity.[194] Finally, the upregulation of IL-25 was demonstrated in an oxazolone-induced intestinal colitis model, and administration of the neutralizing antibody improved the clinical outcome.[131]

Although no data have been published on specific inhibition of IL-25 in clinical settings, indirect evidence for its clinically relevant role comes from studies evaluating brodalumab, a humanized anti–IL-17RA antibody. Approved for the treatment of psoriasis, brodalumab has been identified as the only IL-17A–inhibiting biologic for which no significant difference could be shown when compared with the IL-23 inhibitors risankizumab and guselkumab, the 2 drugs showing highest efficacy in 1 of the 2 network meta-analyses referenced above.[195] The efficacy of anti–IL-17RA brodalumab is very high,[196,197] possibly because IL-17RA neutralization blocks binding to all known heterodimeric receptors for IL-17A/F, but also IL-25 and IL-17C. All these observations regarding IL-25 help clarify the involvement of the other members of the IL-17 family in psoriatic inflammation and better explain the mechanism of action of therapies targeting the IL-17s' common receptor subunit IL-17RA.

The blockade of the IL-17RB subunit or IL-25 itself should be considered in future trials.[198] This may be of particular interest in clinical settings, where there is evidence for a pathogenic role of IL-25, but clinical studies using currently available molecules against other targets had negative results. For instance, in a randomized, double-blind, placebo-controlled trial on the efficacy of brodalumab in individuals with moderate to severe asthma currently taking inhaled corticosteroids, the lung function or asthma symptoms did not improve by blockade of IL-17RA.[199]

Taken together, the reports from mice studies suggest that IL-25 may be a therapeutic target not only for T_H2-associated inflammatory diseases but also for diseases of different pathogeneses such as T_H17-mediated conditions in the skin.

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