



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Review Article

IL-24: A new player in the pathogenesis of pro-inflammatory and allergic skin diseases

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ARTICLE INFO

Article history:

Received 18 September 2019

Received in revised form

29 November 2019

Accepted 2 December 2019

Available online xxx

Keywords:

Allergy

Atopic dermatitis

IL-20 family cytokines

IL-24

Type 2 immunity

Abbreviations:

MDA, melanoma differentiation-associated;

AD, atopic dermatitis; IL-20R, IL-20

receptor; IL-20RA, IL-20R α chain; IL-20RB, IL-20R β chain; IL-22RA1, IL-22receptor α 1 subunit; JAKs, Janus kinases;

STAT, subsequently signal transducer and

activator of transcription; ChIP, chromatin

immunoprecipitation; PPD, para-

phenylenediamine; OAs, oncolytic

adenoviruses; TGF- α , transforming growthfactor- α ; ROS, reactive oxygen species;

CSU, chronic spontaneous urticaria;

ASST, autologous serum skin test;

DNFB, 2,4-dinitrofluorobenzene;

CHS, contact hypersensitivity;

MRSA, methicillin-resistant *Staphylococcus**aureus*

ABSTRACT

Interleukin (IL)-24 is a member of the IL-20 family of cytokines and is produced by various types of cells, such as CD4⁺ T cells, NK cells, mast cells, keratinocytes, bronchial epithelial cells, and myofibroblasts. Previous studies suggest that IL-24 plays an essential role in the pathogenesis of pro-inflammatory autoimmune disorders such as psoriasis, arthritis, and inflammatory bowel diseases. However, the role of IL-24 in the pathogenesis of allergic diseases has been elusive. It has already been reported that IL-24 is involved in the pathogenesis of allergic lung and skin diseases. Moreover, we have recently revealed for the first time the pivotal functions of IL-24 in IL-13-mediated skin barrier dysfunction in atopic dermatitis (AD), which is known to be a characteristic of AD caused by Th2 cytokines such as IL-4 or IL-13. In this review, we show recent advances in the basic characteristics of IL-24 and its novel functions in the pathogenesis of allergic skin inflammation, focusing on AD. A better understanding of the role of IL-24 in allergic diseases can lead to the development of new therapeutic options.

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Introduction

The interleukin (IL)-24 gene was initially isolated from cultured human melanoma cells stimulated with interferon- β (IFN- β) and the protein kinase C activator, mezerein in 1996 and was named

melanoma differentiation-associated (MDA)-7 antigen.¹ Thereafter, because MDA-7 was characterized as a multifunctional cytokine belonging to the IL-20 family, which is a part of the IL-10 family, MDA-7 was renamed IL-24.^{1,2} Earlier studies suggested that IL-24 is a mediator that is crucial for optimal wound healing and for the development of pro-inflammatory autoimmune disorders such as psoriasis, arthritis, and inflammatory bowel diseases.^{3–6} However, the involvement of IL-24 in the pathogenesis of allergic diseases has been largely unknown. Recently, we revealed that IL-24 has a crucial role in the pathogenesis of atopic dermatitis (AD). In this

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Peer review under responsibility of Japanese Society of Allergology.

<https://doi.org/10.1016/j.alit.2019.12.003>

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review, we show the characteristics of IL-24 regarding signal transduction pathways and functions in wound healing and infectious diseases. Furthermore, we introduce how IL-24 contributes to the development of pro-inflammatory and allergic diseases, particularly AD.

Characteristics of IL-24

IL-20 family cytokines and their receptors

The human IL-24 gene consists of seven exons and six introns that are located on chromosome 1q32–33, within the cytokine cluster containing the IL-19 and IL-20 genes, while the IL-22 and IL-26 genes are located on chromosome 12q15.^{2,7–9} The length of IL-24 mRNA is 1718 base pairs encoding 206 amino acids.⁷ The sequence alignment of amino acids shows that IL-24 and the other members of the IL-20 family cytokines share overall homologies ranging from 24 to 33%.^{10,11} These cytokines belong to the IL-20 family based on their usage of common receptor subunits and similar biological functions.^{10,11} There are four types of IL-20 receptors, and the IL-24 signal is transduced through two different heterodimeric receptors. One IL-24 receptor is the type I IL-20 receptor (IL-20R), which is composed of the IL-20R α chain (IL-20RA) and the IL-20R β chain (IL-20RB), and this receptor shares IL-19 and IL-20 as ligands. Both IL-24 and IL-20 can also transduce additional signals through the type II IL-20R composed of IL-20RB and the IL-22 receptor α 1 subunit (IL-22RA1). The receptors for IL-22 and IL-26 consist of IL-22RA1 and IL-20RA, respectively, and both receptor share IL-10RB (Fig. 1).^{12–14} Therefore, four heterodimeric receptors are currently identified as functional receptors for IL-20 family cytokines. Both type I and type II IL-20 receptors are expressed on non-immune cells, such as keratinocytes and bronchial epithelial cells, but not on immune cells. Thus, it is thought that IL-24 fails to activate immune cells.^{15,16} Recently, Ha *et al.* showed the IL-24 and IL-19 signaling suppressed the dermal production of the CCL2 via IL-20RB and thereby reduced CCL2-driven infiltration of inflammatory cells in imiquimod induced psoriatic inflammation.¹⁷ Although both IL-24 receptors (type I and type II IL-20 receptors) are more highly expressed in skin than in bone marrow, the expression of IL-22RA1 in keratinocytes is approximately ten times higher than that of IL-20RA.^{11,15} This finding suggests that IL-24 acts on keratinocytes primarily via the type II IL-20 receptor (IL-22RA1/IL-20RB). It is currently unclear why keratinocytes express type I and type II IL-20 receptors at different levels.

The binding of IL-20 receptors with IL-24 initially activates Janus kinases (JAKs) and subsequently signal transducer and activator of transcription (STAT) 3. IL-24 can induce STAT3 phosphorylation without inducing phosphorylation of other STAT proteins in keratinocytes and bronchial epithelial cells.^{18–20} Andoh *et al.* reported that IL-24 stimulation causes phosphorylation of JAK1 and STAT3 but not JAK2 and STAT1 in colon epithelial cells.⁶ It has been reported that IL-24 activates STAT1 in addition to STAT3 in some cells other than keratinocytes and other epithelial cells,^{10,13,21} although the roles of STAT1 activation by IL-24 in these cells are unclear.

IL-24-producing cells

Numerous cytokines—type 1 cytokine IFN γ ; type 2 cytokines IL-4 and IL-13; Th17 cytokine IL-17A; Th22 cytokine IL-22; and pro-inflammatory cytokines IL-1 β , IL-6, and TNF α —can induce IL-24 (Table 1).^{4,15,18,22} Among these cytokines, the effects of type 2 cytokines on IL-24 production are well studied. Bao *et al.* found that IL-4-transgenic mice spontaneously develop chronically pruritic inflammatory skin lesions, and IL-24 expression is upregulated by several hundred-fold in these lesions compared to wild-type mice.²³ Of interest, Wei *et al.* identified by a chromatin immunoprecipitation (ChIP) sequence-based assay that the IL-24 gene is one of the most highly activated genes by STAT6 in Th2 cells and classified the IL-24 gene as a dominant Th2 lineage-specific gene, along with the IL-4, IL-4 receptor α , and GATA3 genes.²⁴ The underlying mechanism of IL-24 gene expression is now being clarified. In Th2 cells, STAT6 and c-Jun control the transcription of IL-24 downstream of phorbol-12-myristate-13-acetate/ionomycin via the proximal promoter region of the IL-24 gene located between –157 and +95 base pairs of the gene. However, this region does not contain the consensus STAT6-binding sequence (TTCNNN(N)GAA).²⁵ Likewise, keratinocytes and bronchial epithelial cells produce IL-24 in a STAT6-dependent manner.¹⁹ Van Belle *et al.* showed that painting ear skin with para-phenylenediamine (PPD) causes an increase in IL-24 production in CD45⁺Krt10⁺ cells (keratinocytes) but not in CD45⁺ leukocytes.²⁶ In addition to these cells, it has been reported that myofibroblasts, B cells, monocytes/macrophages, mast cells, and NK cells produce IL-24.^{1,6,16,19,25,27–31} Thus, it is assumed that IL-24 is produced by both immune cells and non-immune cells in various situations (Table 1). Recently, Dabitao *et al.* reported that IL-24 and IL-10 are co-expressed but independently regulated in NK cells and macrophages. STAT6 is required for IL-4/IL-13-induced IL-24 expression in both cells. In addition, NK-

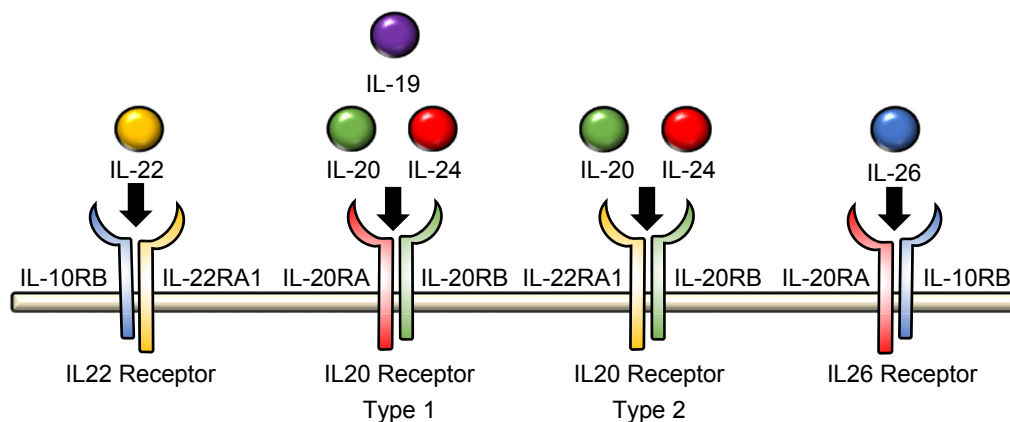


Fig. 1. The IL-20 family cytokines and their receptors. The receptors for IL-20 family cytokines (IL-19, IL-20, IL-22, IL-24, and IL-26) consist of IL-20RA, IL-20RB, IL-22RA1, and IL-10RB. IL-24 transduces intracellular signals through two types of heterodimeric receptor complexes (IL-20RA/IL-20RB and IL-22RA1/IL-20RB).

specific IL-24 expression was also dependent on both type I IFN receptor signaling and STAT4. Induction of IL-24 expression may have different mechanisms in each cell types.³¹

The role of IL-24 in tissue repair and infection

As mentioned above, IL-24 was initially identified as one of the genes expressed in terminally differentiating melanoma cells.¹ The anti-tumor effects of IL-24 are well-defined and IL-24 administration have displayed significant clinical activity in patients with multiple advanced cancers in a phase I/II clinical trial (reviewed in Refs.^{32,33}). Apart from anti-tumor functions, IL-24 also induces several functions in normal cells.

Wound healing

It has been shown that IL-24, as well as other IL-20 subfamily cytokines such as IL-19, IL-20, and IL-22, is upregulated in wounded skin. In an experimental murine dermal wound model, IL-24 expression was detected in keratinocytes located at the wound edge two days after wounding, followed by a peak levels at the sixth day that returned to the original level by the tenth day.³⁴ Keratinocytes stimulated by IL-20 family cytokines secrete various chemokines and antimicrobial peptides to reduce infection and accelerate inflammation. These cytokines can further induce the expression of VEGFA, followed by promoting angiogenesis and neovascularization during wound healing.³⁵ Based on these findings, IL-20 family cytokines stimulate murine keratinocytes to promote tissue repair. Subsequent studies also showed that peritoneal injection of IL-20, IL-22, or IL-24 can accelerate epithelial closure of wound healing in diabetic mice.³⁴ Consistent with this finding, deficiency in IL-22RA1, a receptor subunit shared by IL-20, IL-22, and IL-24, results in delayed wound closure.³⁴ Moreover, IL-24-transgenic mice manifest many similar phenotypes to that of IL-20 and IL-22.³⁶ Thus, these data suggest that the roles of IL-20, IL-22, and IL-24 on cutaneous wound repair in mice are redundant.^{34,36}

In contrast to mice, the role of IL-24 in accelerating wound repair may remain controversial in humans. Tan *et al.* reported that IL-24 decreases microtubule formation in endothelial cells and inhibits angiogenesis.³⁷ Another group reported that production of VEGF and basic fibroblast growth factor, both of which promote angiogenesis, are inhibited by IL-24 overexpression in adenocarcinoma cells derived from human alveolar basal epithelial cells.³⁸ In addition, Poindexter *et al.* reported that IL-24 inhibits transforming

growth factor- α (TGF- α)—induced proliferation and migration of human keratinocytes in an *in vitro* model of wound repair by scratching a monolayer of NHEKs.³⁹ Similarly, Bosanquet *et al.* reported that IL-24 enhances wound chronicity by inhibiting the migration of human keratinocytes through an AKT-dependent pathway.⁴⁰ Thus, these studies suggest that IL-24 can suppress angiogenesis and inhibit the migration of human keratinocytes, followed by a deceleration in wound closure.

Interestingly, exogenous overexpression of IL-24 can selectively inhibit proliferation of human keloid fibroblasts and induce significant apoptosis in these cells.⁴¹ Therefore, treatment of fibroblasts with IL-24 might be considered a new and effective way to improve keloids. In the process of wound healing, IL-24 has different functions depending on cell type and stage of the process. Further investigations will be required to clarify why these discrepancies occur.

Bacterial and viral infection

It has been reported that IL-24 and other IL-20 family cytokines, such as IL-19 and IL-20, have an immunosuppressive role in the skin microbiota.⁴² These cytokines suppress IL-1 β expression in keratinocytes, followed by a reduction in IL-17A expression in T cells. It is assumed that IL-20 family cytokines suppress IL-17A-dependent recruitment of neutrophils, which increases the susceptibility of AD skin to infection by methicillin-resistant *Staphylococcus aureus* (MRSA).⁴² Consistent with this report, IL-24, along with IL-10 and IL-19, downregulates the expression of Th1/Tc1 and Th17/Tc17 cytokines in CD4⁺ and CD8⁺ T cell subsets after tuberculosis infection. They concluded that the IL-20 family cytokines as well as IL-10 play a crucial role in the downregulation of T cell-mediated immune responses in active tuberculosis.⁴³ Moreover, Kumar *et al.* reported that systemic levels of IL-24, together with IL-19 and IL-20, were significantly increased in patients with active pulmonary tuberculosis.⁴⁴ However, some recent studies reported the opposite role of IL-24 in tuberculosis infection. Sa *et al.* showed that IL-20 family cytokines, including IL-24, induce expression of antimicrobial peptides, such as S100A7 in the human epidermis.⁴⁵ This suggests a protective role of IL-24 against bacterial infection.

Concerning viral infection, IL-24 is one of the most upregulated and differentially expressed genes in the lungs of mice infected with H5 avian influenza virus.⁴⁶ Infection of human lung adenocarcinoma cells with influenza A virus increases the expression of IL-24 at both the mRNA and protein levels, which in turn decreases

Table 1
Summary of IL-24 producing cell and the induction.

Species		Cell source	Stimuli	Reference
Human, Mouse	Non-immune cells	Keratinocyte	IFN- γ , IFN- β , IL-4, IL-13, IL-31, IL-17A, IL-22, IL-6, IL-1 β , TNF α , TGF α , SLS, UVB, Injury	18, 19, 22, 39, 40, 41
Mouse		Keratinocyte	TNF, IMQ, Para-phenylenediamine	4, 17, 26
Human, Mouse		Kidney epithelial cell, Bronchial epithelial cell	IL-4, IL-13	53, 55
Human	Immune cells	Myofibroblast	IL-1 β , LPS, TNF- α , IL-17A	6, 21
Human		Melanoma cell	IFN- β + Mezerein	1
Human		Endothelial cell (RA patients)		52
Human		Monocyte/Macrophage (RA patients)		52, 54
Human		Monocyte, T cell	LPS, IFN- γ , anti-CD3 and anti-CD28 antibodies	16
Mouse		Macrophage	LPS, IL-4, IL-13	31
Mouse		NK cell	IL-2, IL-4, IL-12, IFN- α	31
Human		Mast cell	mvT*	29
Human		B cell	Anti-IgM, CD40L	30
Mouse		Th2 cell	PMA	25, 28

IFN, interferon; TNF, tumor necrosis factor; TGF, transforming growth factor; SLS, sodium lauryl sulfate; IMQ, imiquimod; RA, rheumatoid arthritis; LPS, lipopolysaccharide; mvT*, microvesicles derived from activated T cells; PMA, phorbol 12-myristate 13-acetate.

viral replication by activating IFN-mediated anti-viral signaling.⁴⁷ Alternatively, IL-24 also works as a sensitizer and promotes influenza A-induced apoptosis via the toll-like receptor 3 (TLR3)/caspase-8 axis.^{48,49} Although the functions of IL-24 in the host defense against bacterial and viral infection have yet to be fully elucidated, IL-24 might work for downregulation of innate immunity.

Pathogenic roles of IL-24 in pro-inflammatory autoimmune diseases and allergic disorders

Pro-inflammatory autoimmune diseases

It has been shown that IL-24 is upregulated in the psoriatic epidermis.^{4,50} Moreover, He *et al.* previously demonstrated that IL-24-transgenic mice are born exhibiting pathological psoriasis-like skin inflammation.³⁶ STAT3 is overexpressed and activated in psoriatic skin, and expression of constitutively active STAT3 in epidermal keratinocytes causes psoriasis-like skin inflammation in mice.^{4,51} TNF-induced IL-24 expression in the epidermis is essential for the development of psoriasis-like skin inflammation in mice with skin-specific deletion of the IKK β gene (*K14-Cre Ikk2^{fl/fl}*).⁴ In this model, reactive oxygen species (ROS)-mediated activation of ERK induces epidermal IL-24 expression.⁴ Similarly, keratinocytes from psoriasis patients show higher expression of IL-24 than those from control patients.¹⁵ Collectively, these studies suggest that IL-24 is a pivotal mediator in the pathogenesis of psoriasis.

Unlike the case of psoriasis, IL-24 may have a suppressive function on mucosal inflammation in ulcerative colitis and Crohn's disease. Andoh *et al.* reported significant upregulation in IL-24 expression in active lesions from these patients. IL-24 acts on colon epithelial cells to produce mucins that protect the mucosa from excessive inflammation in inflammatory bowel diseases.⁶ Although it has been shown that the expression of IL-24 is upregulated in rheumatoid arthritis and polycystic kidney disease, the physiological function of IL-24 in these disorders remains unclear.^{52–54}

Allergic diseases

Allergic rhinitis and allergic asthma

Zissler *et al.* reported that IL-4 induces IL-24 expression in normal human airway epithelial cells.⁵⁰ This group also reported that the expression of IL-24 is significantly elevated in nasal scrapings from allergic rhinitis patients compared with those of healthy controls. Moreover, the same group reported that the IL-24 level in sputum is increased in seasonal asthmatic patients.⁵⁶ Interestingly, IL-24 expression in these patients is moderately correlated between the upper and lower airways. Thus, IL-24 might be a representative nasal proxy biomarker for whole-airway allergic inflammation. However, the functions of IL-24 in allergic airway inflammation have yet to be fully elucidated despite the high expression of IL-24 in allergic rhinitis and allergic asthma.

Chronic spontaneous urticaria

It is believed that anti-IgE therapy is very effective for chronic spontaneous urticaria (CSU).⁵⁷ Therefore, IgE that is reactive to self-antigens such as thyroid antigens and double-stranded DNA may play an important role in the pathogenesis of CSU. Schmetzer *et al.* identified anti-IL-24 IgE as a common and specific autoantibody in CSU patients. Moreover, anti-IL-24 IgE levels in serum show a good association with disease severity. Interestingly, IL-24 induces the release of histamine from human mast cells sensitized with purified IgE of patients with CSU but not of control subjects,⁵⁸ suggesting that IL-24 acts as an autoantigen. Similarly, de Montjoye *et al.* reported that expression of the IL-24 gene and protein is increased in PBMCs in a subpopulation of CSU patients. This group

showed that IL-24 expression is positively correlated with both IL-6 expression and disease severity, suggesting that it plays a role in the onset of CSU.⁵⁹

Yu *et al.* reported that autohemotherapy can provide clinical benefit in part by its effects on the levels of IgE autoantibodies in CSU patients who are positive for the autologous serum skin test (ASST). In addition, anti-IL-24 IgE levels were significantly decreased only in the responders to autohemotherapy.⁶⁰ These findings suggest that IgE autoantibodies against IL-24 might be involved in the underlying mechanisms of autohemotherapy in CSU. Further studies are needed to determine the function of anti-IL-24 IgE in CSU.

Allergic contact dermatitis

It was reported that expression of IL-24 and IL-19 is elevated in a mouse model of allergic contact dermatitis induced by painting skin with 2,4-dinitrofluorobenzene (DNFB).¹⁵ Consistently, Van Belle *et al.* reported that IL-24 expression is increased in PPD-induced allergy patients.²⁶ Moreover, genetic deficiency in IL-24 partially protected against the contact hypersensitivity (CHS) induced by PPD. This group showed that the PPD-induced recruitment of CD45⁺ cells and neutrophils into the skin was reduced in IL-24-deficient mice. As mentioned earlier, IL-20 receptors are expressed on non-immune cells, including keratinocytes, but not on immune cells. Taken together, IL-24 plays an important role in PPD-induced CHS by inducing acanthosis and the production of chemokines in keratinocytes. Thus, IL-24 is a crucial mediator for the development of allergic contact hypersensitivity.²⁶

Atopic dermatitis

Atopic dermatitis is a chronic, eczematous, and severely pruritic skin disorder characterized by IgE elevation and skin barrier dysfunction and is widely accepted to be caused by type 2 cytokines such as IL-4, IL-5, and IL-13.⁶¹ AD patients show abnormal skin barriers, which are frequently colonized with *S. aureus*.^{62,63} Epithelial barrier dysfunction is essential to initiating or accelerating AD by increasing the exposure of the immune system to allergens. Colonization by *S. aureus* in the AD skin alters the T cell responses via Langerhans cells and causes Th2-shifted immune responses (reviewed in Ref⁶³).

We and other groups found that IL-24 has crucial roles in barrier dysfunction and *S. aureus* infection. IL-4 and IL-13 can down-regulate the barrier function of the skin by reducing expression of filaggrin, which is essential for both terminal differentiation of keratinocytes and the barrier function of skin, probably via STAT3.⁶⁴ We previously showed that genetic deficiency of periostin, a matricellular protein produced by non-immune cells stimulated by IL-4/IL-13, decreases AD-like skin inflammation by protecting epithelial barrier dysfunction in a mouse model of allergic skin inflammation induced by painting skin with house dust mite (HDM).^{65,66} However, it had remained unclear how type 2 cytokines cause barrier dysfunction via periostin. Using DNA microarray analysis, we found that the expression of several mediators induced by IL-13 stimulation in murine embryonic fibroblasts requires periostin. IL-24 was included among these mediators. We confirmed that periostin is also required for IL-24 expression in human keratinocytes stimulated with IL-13. STAT6 silencing in human keratinocytes significantly decreases IL-13-dependent expression of IL-24 and periostin. This suggests the importance of the IL-13/STAT6 pathway for the expression of IL-24 and periostin in human keratinocytes. However, it is still unclear how periostin upregulates the expression of IL-24. Further investigation will need to clarify the underlying mechanism.

Cornelissen *et al.* reported that IL-24 and IL-20 produced in IL-31-stimulated keratinocytes cooperatively downregulate the

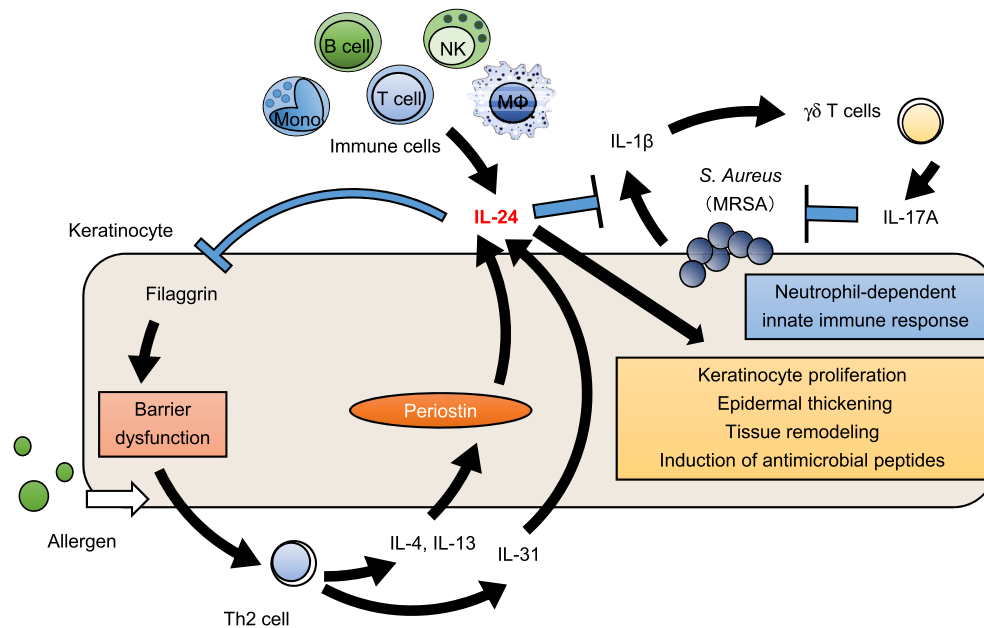


Fig. 2. Schematic model of novel mechanisms by which IL-24 causes barrier dysfunction and suppression of innate immune response in AD. In type 2 inflammatory conditions, IL-24 is produced by keratinocytes downstream of IL-4, IL-13, and IL-31 and immune cells. IL-24 downregulates filaggrin expression, leading to barrier dysfunction. IL-24 contributes to psoriasis-like epidermal alterations. Moreover, IL-24 suppresses the expression of IL-1 β , followed by the attenuation of IL-17A-dependent recruitment of neutrophils induced by *S. aureus* infection. Suppression of neutrophil-dependent innate responses increases the susceptibility of AD skin to infection by *S. aureus*.

expression of filaggrin.²² Consistent with this report, we also showed that IL-24, as well as IL-13, can downregulate the expression of filaggrin in a three-dimensional reconstructed epidermis. Surprisingly, IL-24 silencing markedly reversed the IL-13-induced downregulation of filaggrin expression, suggesting that IL-24 is a pivotal mediator for IL-13-dependent downregulation of filaggrin expression. As mentioned above, IL-24 activates STAT3 but not STAT6 in epithelial cells. It is noteworthy that knockdown of STAT3 but not STAT6 nearly restores IL-24-induced downregulation of filaggrin expression in keratinocytes. We also found that STAT6 and periostin are essential for the upregulation of IL-24 and STAT3 expression and the downregulation of filaggrin expression in HDM-induced AD-like skin in mice. More importantly, expression of both IL-24 and periostin is enhanced in the epidermis of skin tissues from AD patients. From these results, we propose that the IL-13/periostin/IL-24 pathway is a novel mechanism for barrier dysfunction. IL-13 induces IL-24 production via STAT6 and periostin in keratinocytes. Then, IL-24 downregulates filaggrin expression via STAT3. Thus, IL-24 contributes to barrier dysfunction downstream of the IL-13/periostin signals in AD.

As already mentioned above, Myles *et al.* found that IL-24 suppresses IL-1 β expression in keratinocytes, followed by a reduction in IL-17A expression in $\gamma\delta$ T cells and recruitment of neutrophils to the skin.⁴² Thus, these findings suggest that increased IL-24 expression in the keratinocytes contributes to the colonization of *S. aureus* in AD skin.

Noda *et al.* found that Asian AD patients show a unique immune phenotype, combining the characteristics of AD and psoriasis.⁶⁷ As mentioned above, it has been reported that the psoriatic epidermis shows upregulation of IL-24,⁴ and activated STAT3 causes psoriasis-like skin inflammation in mice.^{36,51} Thus, these findings may imply that IL-24 contributes to psoriasis-like features in AD skin.

Collectively, IL-24 plays an important role in barrier dysfunction downstream of type 2 inflammation, colonization by *S. aureus*, and the induction of psoriasis-like inflammation in AD skin (Fig. 2). Thus, IL-24 is a pivotal mediator for the development of AD.

Conclusion

The number of studies focusing on the physiological functions of IL-24 in human disease is increasing since IL-24 has been characterized as a member of the IL-20 family cytokines. As highlighted in this review, IL-24 is a novel key mediator for both pro-inflammatory diseases and allergic disorders. Indeed, epidermal IL-24 expression is upregulated in AD. IL-24 is produced by Th2 lymphocytes and keratinocytes stimulated by type 2 cytokines such as IL-4, IL-13, and IL-31. IL-24 downregulates filaggrin expression in keratinocytes downstream of the IL-13/periostin pathway. Moreover, IL-24 might contribute to the immune evasion of *S. aureus* and the induction of psoriatic inflammation in AD skin. The pathological importance of IL-24 in allergic diseases, including AD, has certainly emerged. Nevertheless, the roles of IL-24 in allergic diseases are not fully understood. Therefore, we hope that further investigations will be performed to deepen our understanding of the roles of IL-24 in allergic diseases.

Acknowledgments

We thank our collaborators for contributing to the present article: Prof. Simon J Conway at Indiana University; and Drs. Gaku Tsuji, Takeshi Nakahara, and Akiko Hashimoto-Hachiya at Kyushu University; and Drs. Yasuhiro Nanri, Masahiro Ogawa, Tomohito Yoshihara, and Miho Masuoka at Saga Medical School. The first author (YM) received the 2018 JSA Best Presentation Award by the Japanese Society of Allergy for the work.

Conflict of interest

The authors have no conflict of interest to declare.

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