



Revisiting murine models for atopic dermatitis and psoriasis with multipolar cytokine axes

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Atopic dermatitis (AD) and psoriasis are one of the common skin diseases. Animal models are a powerful tool to analyze these diseases, which are complicated by multiple cytokine pathways. However, many discrepancies between the human diseases and murine models have been noticed. Therefore, investigators should be aware of the differences between the murine AD models and human AD when translating murine data to human skin diseases. This review highlights the differences between the inflammatory profiles between murine models and human diseases focusing on AD and psoriasis.

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Introduction: animal models and their importance

Atopic dermatitis (AD) is caused by interaction between immune system and skin barrier system [1–10]. In addition, multiple cytokine pathways are involved in the skin inflammation in AD. Besides the immune disequilibrium, reduced expression of *skin* barrier components characterizes the pathogenesis of AD [1,2,8–10]. To analyze this complex disease, animal models can be a powerful tool.

Transcriptomic analyses of the skin from patients with AD at the baseline and after treatment has advanced our knowledge of AD [11–15]. As expected, the critical role of T helper type 2 (Th2) axis and its dominance have been confirmed. However, this rather simple view is now challenged by a new line of evidence.

Human AD can be stratified into several subtypes by several biomarkers. Increased levels of total serum IgE and the presence of specific IgE against environmental and food allergens are observed in about 80% of AD, which is categorized as extrinsic or allergic AD [16]. The remainder, called intrinsic or non-allergic AD, exhibits normal total IgE levels, absence of specific IgE, and poor infiltration of eosinophils in the skin, despite the activation of Th2-type skin immunity [16,17]. The morphology and distribution of skin lesions show age-related changes [18]. In infants, AD lesions are acute and tend to lie on the face, the trunk, and the limbs [18]. AD in adolescents starts to present lichenification (thickness of the epidermis) at flexures, an indication of chronic dermatitis [18]. Adult type AD often presents with prurigo-like lesions [18]. Immunophenotype of peripheral blood lymphocytes can be transmuted with ageing from a Th2-dominated pattern in infants with AD into a state superimposed with Th22/Tc22-cytokines in adults with AD [19^{••}]. In chronic lesions of AD, some Th1-associated genes such as *Mx1*, *Cxcl9*, *Cxcl10*, and *Cxcl11* are increased and keratinocytes show susceptibility to IFN- γ -mediated apoptosis [20,21^{••}]. Dysregulated apoptosis is related to the spongiosis of the epidermis, which is a main feature of eczema [22]. Furthermore, Asian (Japanese and Korean) patients with AD show a combination of interleukin (IL)-23/Th17 and Th22 pathways, a feature of psoriasis vulgaris [23^{••}]. Therefore, AD is an entity encompassing different conditions of skin inflammation or endotypes, which are related to underlying variations in immunological mechanism, disease course, and genetic makeup.

Above findings prompted researchers to re-evaluate murine AD models, such as NC/Nga, flaky tail, *Fc γ* -mutated, ovalbumin-challenged, oxazolone-challenged, and IL-23-injected mice, in the scope of transcriptomic profiles [24^{••}]. The result clearly indicated that none of these murine models fully represented all aspects of the human AD profile whereas IL-23-injected mice that had been considered as a murine psoriasis model simulated the human AD the best [24^{••}]. Thus, investigators should be aware of the differences between the murine AD models and human AD when translating murine data to human skin diseases.

This review highlights the differences between the inflammatory profiles between murine AD models and human AD and discuss the pathogenesis of AD and psoriasis in the spectrum of dermatitis.

Murine models of AD

Clinical findings of murine models of AD include hyperplasia of the epidermis, decreased skin barrier, pruritus, scratching behavior, and increase in serum IgE, all of which represent the features of human AD. However, human AD can be stratified into several distinct types by the age, chronicity, or genetic background of the patients [19^{••},23^{••},25^{••},26^{••},27] (Figure 1).

Flaky tail mice

Flaky tail mice (*ma/ma Flgft/ft*) have a frameshift mutation in *Flg* (*Flgft/ft*) and also carries a mutation in *Tmem79/Matt* (*Tmem79ma/ma*), which causes no expression of mattrin, conferring a matted hair phenotype called matted [28].

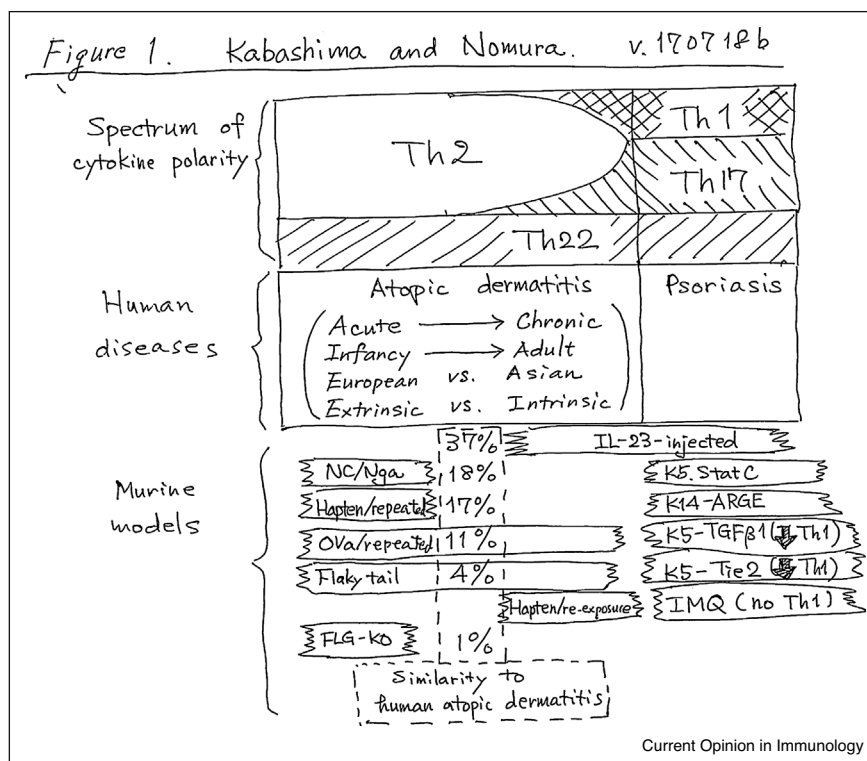
Flaky tail mice have a defective skin barrier, with increased percutaneous transfer of antigens and chemical haptens [29]. Topical application of *Dermatophagoides*

pteronyssinus extract on the steady state skin of Flaky tail mice induces human AD-like dermatitis accompanied with increased serum IgE [29]. The mRNA expression levels of interferon (IFN)- γ , IL-4, and IL-13 were similar between Flaky tail mice and B6 mice, but there was an enhancement in the IFN- γ and IL-17 mRNA expression [29–31]. Of note, spontaneous development of AD-like dermatitis and IgE induction are attenuated by IL-17A deficiency in flaky-tail mice [32[•]]. The skin inflammation is associated with cutaneous expansion of IL-5-producing group 2 innate lymphoid cells [33].

Filaggrin-knockout mice

Because loss-of-function mutations in filaggrin are major predisposing factors for AD in humans, filaggrin-null *Flg* (–/–) mice have been generated and backcrossed onto C57BL/6 and BALB/c [34]. Newborn *Flg* (–/–) mice exhibit dry scaly skin as seen in human AD. Despite

Figure 1



Complexity of cytokine polarity in human atopic dermatitis (AD) and psoriasis. Human AD can be stratified into subtypes by the chronicity of the lesions (acute or chronic), age (infancy or adult) and genetic background (European or Asian) of the patients, and presence or absence of serum hyper-IgE (extrinsic or intrinsic, respectively). Dominance of Th2 cytokines is a feature of human AD, especially in the lesions of acute phase or infant, European, and extrinsic types. However, Th1 and Th17 cytokines are often superimposed in the lesions of chronic phase and adult, Asian, and intrinsic types. The cytokine profile of human psoriasis is monotonously dominated by Th17 and Th1 types. Th22 type cytokines are increased in both AD and psoriasis, probably affecting the epidermal homeostasis, such as acanthosis and production of antimicrobial peptides. Various murine models for AD and psoriasis are available. However, none of these fully recapitulates the features of corresponding human disease. IL-23-injected mice, showing a similarity of 37% to human AD, exhibit a mixture of AD and psoriasis in cytokine polarity. NC/Nga and Hapten/repeated models show Th2-dominant pattern. OVA/repeated and Flaky tail mice show activation of multiple cytokine axes including Th1 and Th17. Hapten/re-exposure induces activation of Th1/Th17, which might reflect the very early phase of human AD or allergic contact dermatitis. *Filaggrin* (–/–) mice show poor inflammatory response under normal condition. Models for psoriasis, such as K5.StatC, K14-ARGE, K5-TGF β 1, K5-Tie2, and imiquimod (IMQ)-applied mice, are varied if the transcripts are closely analyzed.

the decrease in natural moisturizing factor levels (the final products of filaggrin), stratum corneum is well hydrated and transepidermal water loss is normal in adult *F/lg(-/-)* mice [34]. Under the specific pathogen free condition, *F/lg(-/-)* mice do not exhibit spontaneous skin inflammation. However, repeated percutaneous application of ovalbumin (OVA) results in higher serum levels of OVA-specific IgG1 and IgE, both of which are markers for the Th2-type response [34]. The facilitated antigen penetration through the filaggrin deficient stratum corneum exaggerates responses to irritants (croton oil), haptens such as dinitrofluorobenzene (DNFB), and protein antigens, including Th1 and Th2 responses, in *F/lg(-/-)* skin [34]. The polarity of cytokine profiles in the skin of *F/lg(-/-)* mice requires further investigation.

Epicutaneous ovalbumin exposure model

This model mimics multiple extrinsic allergen exposures, which is considered to occur in patients with AD. Typically, BALB/c mice are epicutaneously exposed to ovalbumin for 3 weeks; each week being separated by a 2-week resting period. This procedure results in a rise in total and antigen-specific serum IgE and leads to the development of a dermatitis characterized by infiltration of T cells, eosinophils, and neutrophils and by local expression of mRNA for the cytokines IL-4, IL-5, and IFN- γ [35–38].

Thickening of the skin is mediated by IFN- γ , IL-4, and IL-5, whereas the infiltration of T cells or eosinophils depends more on IL-4 or IL-5, respectively. Therefore, both Th2 and Th1 cytokines seem to play roles in the inflammation and hypertrophy of OVA-exposed skin [35,36]. Total IgE (a marker of Th2 response) and IgG2a (a marker of Th1 response) arise after the second exposure week, followed by an increase of OVA-specific IgE later. Other cytokines such as IL-1 β , tumor necrosis factor (TNF)- α , IL-10, IL-13, and IL-12p35 also increase and chemokines and their receptors for both Th1 and Th2 cells are up-regulated [37].

Hapten-challenged mice

Hapten is a low-molecular-weight xenobiotic chemical that penetrates to the skin and chemically reacts with self-proteins. Such formed hapten-self complex is recognized as a neo-antigen and induce allergen-specific effector T cells in allergic contact dermatitis (ACD), a T cell-mediated type IV delayed hypersensitivity reaction [39].

The contact hypersensitivity reaction (CHS) is a cell mediated response to epicutaneously applied haptens or allergens, which simulates human ACD. This reaction consists of two phases. The mice are exposed to a hapten by a location distal to the site of elicitation (sensitization). Typically, following an intermission, mice are subjected to re-exposure (single challenge) to the hapten during the

elicitation phase [40]. Studies on CHS in animals using hapten indicate hapten-specific type 1 CD4⁺ and CD8⁺ T cells (Th1 and Tc1 cells, respectively) act as effectors; whereas Th2 cells function as regulatory elements [41].

In contrast, repeated elicitation of CHS with haptens, such as oxazolone and 2,4,6-trinitrochlorobenzene (TNCB), is often used to induce murine AD-like models. The shift in the time course of antigen-specific response from a delayed-type to an early-type response in this model is reflected as the shift of cutaneous cytokine profiles from a Th1-like (IL-2, IL-3, and IFN- γ) to a Th2-like (IL-4, IL-10, and TNF- α) [42*,43,44]. It accompanies with epidermal hyperplasia, massive accumulation of CD4⁺ T cells beneath the epidermis, and elevation of antigen-specific serum IgE [42*,43,45]. This model emulates some findings of human AD such as pruritic dermatosis with epidermal hyperplasia and aberrant expression of differentiation proteins, filaggrin, loricrin, and involucrin in the epidermis [45].

NC/Nga and NC/Tnd mice

NC/Nga and NC/Tnd mice spontaneously develop itchy skin lesions, which resemble human AD clinically and histologically [46,47]. The skin lesions develop under an air-“un”regulated conventional circumstance from 6 to 8 weeks of age, whereas they do not in air-regulated specific pathogen-free conditions [47]. Serum IgE levels of NC/Nga increase from 8 weeks of age in correlation with disease severity. Mast cells and IL-4 producing CD4⁺ T cells are increased in the skin. Th2 chemokines, such as thymus- and activation-regulated chemokine (TARC), macrophage-derived chemokine (MDC), are overproduced in the lesion [48]; a condition which mimics human AD phenotypes. The overproduction of IgE is explained with a defective IFN- γ production by T cells in response to IL-12 and a low responsiveness of B cells to IFN- γ in NC/Nga mice [49]. The phenotype of NC strains is linked to a region of an unknown function, Derm 1, on chromosome 9 [50].

Dust mite antigen-challenged mice (see also NC/Nga and NC/Tnd)

AD-like dermatitis can be induced by application of crude extract of *Dermatophagoides farinae* at a concentration of 1 or 10 mg/ml, painted 5 times repeatedly at an interval of 7 days onto the ear of NC/Nga or BALB/c mice with or without simultaneous tape-stripping [51]. The inflammatory changes are more evident in NC/Nga mice than in BALB/c mice and potentiated by tape-stripping. The ear swelling is accompanied by increased serum IgE, increased IL-4 mRNA, and decreased IFN- γ mRNA levels.

Assessment of murine AD models

To analyze the complexity of human AD, murine models of AD are essential. However, the fidelity of each AD

model has not been evaluated. Utilizing transcriptomic profiling, 6 common murine models of AD have been compared with the human AD. Transcriptomic profiling was performed by using microarrays and quantitative RT-PCR on biopsy specimens from NC/Nga, flaky tail, *Flg*-mutated, ovalbumin-challenged, oxazolone-challenged, and IL-23-injected mice (Table 1) [24**]. Gene expression data of patients with extrinsic and intrinsic AD, psoriasis, and contact dermatitis were obtained from previous patient cohorts (Table 1) [24**].

Murine models that show the largest homology with a human meta-analysis-derived AD transcriptome are IL-23-injected, NC/Nga, and oxazolone-challenged mice

at 37%, 18%, and 17%, respectively (see the column 'Transcriptome homology to AD [%]' in Tables 1 and 2). Similar to human AD, robust Th1, Th2, and also Th17 activation are seen in IL-23-injected and NC/Nga mice, with similar but weaker inflammation in ovalbumin-challenged mice. Oxazolone-challenged mice show a Th1-centered reaction, and flaky tail mice demonstrate a strong Th17 polarization. *Flg*-mutated mice display filaggrin downregulation without significant inflammation [24**]. Therefore, no single murine model fully captures all aspects of the AD profile; instead, each model reflects different immune or barrier disease aspects. Overall, among the 6 murine models, IL-23-injected mice best simulate human AD (Table 1).

Table 1

Cytokine multiplicity in comparison between mouse atopic dermatitis models and human atopic dermatitis

Model	Th1/Tc1	Th2/Tc2	Hyper-IgE	Th17/Tc17	Th22/Tc22	Th9/Tc9	TNF- α	IL-1 β	IL-6	Transcriptome homology to AD (% of MADAD DEGs [16])	Reference
Flaky tail	Yes ^a	Yes	Yes	Yes ^b	Yes	?	?	Yes	Yes	4%	[24**,29,30,32*]
<i>Flg</i> -mutated ^c	No	No	No ^c	No	No	?	?	No	?	1%	[24**]
NC/Nga; NC/Tnd	Suppressed	Yes	Yes	Yes	Yes	?	?	Yes	?	18%	[24**]
Ova/repeated	Yes	Yes	Yes	Yes	?	?	Yes	Yes	?	11%	[24**]
Hapten/re-exposure	Yes	No	No	?	?	?	No	Yes	Yes	NA	[43]
Hapten/repeated	Suppressed	Yes	Yes	Yes	?	?	Yes	Yes	Yes	17% (oxazolone)	[24**,43]
Human; children	Suppressed	Yes	Yes	No	Less	No	?	?	?	NA	[26**]
Human; adults	Suppressed	Yes	Yes	No	Enhanced	Yes	?	?	?	NA	[26**]
Human; European	Less	Yes	Yes	Less	Less	?	?	?	?	NA	[23**]
Human; Asian	Yes	Yes	Yes	Yes	Yes	?	?	?	?	NA	[23**]
Human; extrinsic	Less	Yes	Yes	Less	Less	Less	?	?	?	NA	[25**]
Human; intrinsic	Higher	Yes	No	Higher	Higher	Higher	?	?	?	NA	[25**]

NA, not available; ?, unknown or not described; MADAD, meta-analysis-derived atopic dermatitis [24**]; DEG, differentially expressed gene [24**].

^a Exaggerated sensitization to ovalbumin [30–31].

^b Attenuated inflammation in the absence of IL-17A [32*].

^c Shows exaggerated Th1/Th2 responses to repeated hapten elicitation.

Table 2

Cytokine multiplicity in comparison between mouse psoriasis models and human psoriasis

Model	Th1/Tc1	Th2/Tc2	Hyper-IgE	Th17/Tc17	Th22/Tc22	Th9/Tc9	TNF- α	IL-1 β	IL-6	Transcriptome homology to AD (% of MADAD DEGs [16])	Reference
K5-Tie2	Yes ^a	?	?	Yes ^b	Yes	?	Yes	No	Yes/No ^c	NA	[60,62**]
IMQ	No	?	?	Yes	Yes	?	No/Yes ^d	Yes	No ^c	NA	[62**,63]
K14-ARGE	Yes	?	?	Yes ^b	Yes/No ^e	?	Yes	Yes	Yes	NA	[62**]
K5.Stat3C	Yes	?	?	Yes ^b	Yes/No ^e	?	Yes	Yes	Yes	NA	[62**,68]
K5-TGF β 1	Yes ^a	?	?	Yes ^b	Yes/No ^e	?	Yes	Yes	Yes	NA	[62**]
IL-23 injected	Yes	Yes	?	Yes	Yes	?	?	Yes	Yes	37%	[62**,70–72]
Human	Yes	No	NA	Yes	Yes	Yes ^f	Yes	Yes	Yes	NA	[54]

NA, not available; ?, unknown or not described; MADAD, meta-analysis-derived atopic dermatitis [16]; DEG, differentially expressed gene [16].

^a Increased *Ifng* but decreased either *Il12a* or *Cxcl11* transcript in K5-Tie2 or K5-TGF β 1, respectively, in a study (see Swindell *et al.*, Figure 13S) [62**].

^b Only marginal increase of *Il17a* transcript in a study (see Swindell *et al.*, Figure 13S) [62**].

^c Decreased or only marginal *Il6* transcript in a study (see Swindell *et al.*, Figure 13S) [62**].

^d Aldara (imiquimod)-induced dermatitis is attenuated in TNF- α deficient mice [63].

^e Only marginal or decreased changes of *Il22* transcript in a study (see Swindell *et al.*, Figure 13S) [62**].

^f Th9 cells are increased in psoriasis and AD [59].

However, we must be careful in interpreting the data and comparing them between mice and human. Firstly, too much focusing on the transcriptome in cytokines may be misleading. The receptor affinity of cytokines as proteins is different. For example, the equilibrium dissociation constant (Kd) between IFN- γ and its receptor (IFN- γ R α) is 10 nM [52]. In the case of IL-4, however, Kd between the IL-4/IL-4R α complex and one of the two low affinity subunits IL-13R α 1 or common γ chain is 1 to 2 μ M [53]. Therefore, less mRNA does not always mean reduction of the biological activity of the corresponding protein. Secondly, mouse models are incapable in reproducing the transition of cytokine profiles in ageing skin lesions of human AD from Th2 to Th1 polarity. Finally, murine models and transcriptomic analyses have not succeeded to evaluate apoptosis of keratinocytes, a major mechanism of eczema/spongiosis formation [22].

Murine models of psoriasis

Psoriasis is one of the most common inflammatory skin disorders in developed countries, especially in Caucasian population [54]. Although the pathogenesis of psoriasis is not fully revealed, effectiveness of biologics against TNF- α , IL-17, and IL-23, clearly indicates a pivotal role of IL-23/Th17 axis on the development of psoriasis [3]. Anti-TNF- α monoclonal antibodies (infliximab and adalimumab) and etanercept (dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 TNF receptor linked to the Fc portion of human IgG1) show a high efficacy for psoriasis. Contribution of the IL-17/IL-23 axis inflammation in psoriasis is evident by the high efficacy of antibodies against IL-23 (ustekinumab [anti-IL-12p40], and guselkumab and tildrakizumab [anti-IL-23p29]), IL-17 (secukinumab and ixekizumab [anti-IL-17A]), and receptor for IL-17 (brodalumab [anti-IL-17RA]) [3,55]. There are numerous mouse models of psoriasis with various degrees of recapitulation [56–58]. Role of Th9 cells, which are increased in psoriasis and atopic dermatitis, is not known [59].

K5-Tie2 mice

K5-tTA-driven conditional expression of Tie2, the endothelial specific receptor tyrosine kinase, in basal keratinocytes leads to the development of a psoriasiform phenotype [60]. Spontaneously developed findings are hallmarks of human psoriasis including acanthosis, increases in dermal CD4⁺ T cells, infiltrating epidermal CD8⁺ T cells, dermal dendritic cells and macrophages, and increased expression of cytokines and chemokines associated with psoriasis, including IFN- γ , TNF- α , and IL-1 α , IL-6, IL-12, IL-22, IL-23, and IL-17. Anti-microbial molecules, cathelicidin, β -defensin, and S100A8/A9, are also up-regulated in the hyperproliferative skin. These features can be reversed by repression of the transgene and improved by systemic cyclosporin A.

Imiquimod applied mice

Topical application of imiquimod (IMQ), a TLR7/8 ligand and potent immune activator, can induce psoriasiform dermatitis [61]. Daily application of IMQ on mouse skin induces inflamed scaly skin lesions resembling plaque-type psoriasis. These lesions show increased epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabscesses, neoangiogenesis, and infiltrates of CD4⁺ T cells, CD11c⁺ dendritic cells, and plasmacytoid dendritic cells. IMQ induces epidermal expression of IL-23, IL-17A, and IL-17F. Disease development is blocked in mice deficient for IL-23 or the IL-17 receptor, indicating a pivotal role of the IL-23/IL-17 axis in this model. *Ifng* is not increased in a genome-wide expression profiling (see Figure S13 in reference [48]) [62^{••}]. On the other hand, IMQ-mediated dermatitis is suppressed in TNF- α deficient mice [63].

K14-ARGE and INV-AR mice

K14-ARGE and INV-AR transgenic mice express human amphiregulin in the basal epidermis by human keratin 14-promoter and in the supra-basal epidermis by human involucrin-enhancer/promoter, respectively [64,65]. These transgenic mice possess a limited lifespan and scaling, papillomatous, erythematous skin with partial alopecia. Furthermore, synovial inflammation appears around 2 to 3 weeks of age, which may mimic psoriatic arthritis. A dermal and epidermal infiltrate is consisted of neutrophils and CD3⁺ T cells. A microarray based profiling of the affected ear and tail skin of K14-ARGE indicates increased expression of *Tnf*, *Ifng*, *Il6*, *Cxcl10*, and *Itgb2*, all of which are disease contributors to human psoriasis [62^{••}].

K5.Stat3C mice

Constitutively activated form of Stat3 (Stat3C) is expressed in epidermal keratinocytes under the control of bovine K5 regulatory sequence in K5.Stat3C mice [66]. These transgenic mice develop a skin phenotype either spontaneously, or in response to wounding, that closely resembles psoriasis. The development of psoriatic lesions in K5.Stat3C mice requires cooperation between Stat3 activation in keratinocytes and activated T cells. Abrogation of Stat3 function by a decoy oligonucleotide inhibits the onset and reverses established psoriatic lesions in this model.

In the 12-*O*-tetradecanoylphorbol-13-acetate-induced psoriasis-like lesions in K5.Stat3C mice, increased transcript levels for IL-23, IL-17A, IL-17F, and IL-22, TNF- α , amphiregulin, HB-epidermal growth factor (EGF), and transforming growth factor (TGF)- α , similar to human psoriasis [67,68].

K5-TGF β 1 mice

Human TGF β 1, a potent keratinocyte growth inhibitor, is overexpressed in keratinocytes under the control of

bovine K5 promoter in K5-TGF β 1 mice, which develop inflammatory skin lesions with appearance of psoriasis-like plaques, generalized scaly erythema, and Koebner's phenomenon [69]. These lesions were characterized by epidermal hyperproliferation, massive infiltration of neutrophils, T cells, and macrophages to the epidermis and superficial dermis, subcorneal microabscesses, basement membrane degradation, and angiogenesis. A microarray study indicates increased expression of *Tnf*, *Ifng*, *IL6*, and *Cxcl10* in the lesion of K5-TGF β 1 mice [62**].

IL-23-injected mice

Intradermal administration of IL-23 initiates a cascade of events resulting in erythema, mixed dermal infiltrates, and epidermal hyperplasia associated with parakeratosis [70]. IL-23 induces IL-17A, IL-22, IL-19, and IL-24 expression in mouse skin, all of which are elevated in human psoriasis [70,71]. The epidermal hyperplasia is dependent on IL-17A and IL-22, but not on IL-19 and IL-24 [70,71]. The psoriasis-like phenotype of this model requires IL-6, which induces expression of IL-22R1A [72]. These data implicate the importance of IL-23 and IL-22 in the pathogenesis of psoriasis.

Assessment of psoriasis murine models

Although clinical appearance of psoriasis vulgaris in humans is characterized by a certain level of uniformity, no single murine model recapitulates all features of the human disease. Thus, five psoriasis mouse models have been evaluated by whole-genome transcriptional profiling (Table 2) [62**]. K5-Tie2, IMQ, K14-AREG, K5-Stat3C, and K5-TGF β 1 mice were selected. For all five models, correspondence to the human disease was strong with respect to genes involved in epidermal development and keratinization. Immune and inflammation-associated gene expression, in contrast, was more variable between models as compared to the human disease (Table 2 and Figure S13 in Ref. [62**]).

The levels of Th1/Tc1-related transcripts vary: *Ifng* is increased in human psoriasis whereas it is decreased in IMQ model, only marginal in K5-Tie2 and K14-AREG (tail lesion), and increased to human level in K14-AREG (ear lesion), K5-Stat3C, and K5-TGF β 1 [62**]. Other Th1/Tc1-transcripts such as *Cxcl1*, *Cxcl9*, *Cxcl10*, and *Cxcl11* are not so increased to the levels of human counterpart, except K14-AREG [62**].

Th2-polarity is not detected in human psoriasis vulgaris, whereas it is not precisely evaluated in most of the murine models for psoriasis except IL-23-injected mice, in which *Il13* transcript was up-regulated to a higher level than that of epicutaneous ovalbumin exposure model and NC/Nga mice (murine models for AD) [24**]. Furthermore, the IL-23 model captures some lipid, tight junction (CLDN8), and water channel (aquaporin 7) deficiencies,

which were reported to characterize the barrier defects in patients with AD [24**].

IL-17/IL-23-axis is increased in all of psoriasis models. However, the increase of *Il17a* transcript is only marginal in K5-Tie2, K14-AREG, K5-Stat3C, K5-TGF β 1 models. *Il22* transcript level is marginal in K5-Stat3C and K5-TGF β and rather decreased in K14-AREG [62**].

These variations in transcript levels reveal the similarities and differences among human psoriasis and its murine models. However, further study is required to confirm these finding at the protein level. Therefore, similar caveats must be noted as discussed in the assessment of murine AD models.

Conclusion

Animal models of AD and psoriasis have promoted our understanding of the complex pathogenesis of human AD and psoriasis and provided us with potential targets for new therapies including biologics. Ongoing clinical trials and whole transcriptomic analyses of human specimens are, in turn, unveiling unexpected similarities between the AD and psoriasis and humans [3]. With the state-of-the-art technologies, applying collective and comprehensive approaches, such as transcriptomics, proteomics, or lipidomics, onto mouse models and human materials is feasible. To continue revisiting and evaluating the current animal models will lead to better utilization of them in proper ways.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Egawa G, Kabashima K: **Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march.** *J Allergy Clin Immunol* 2016, **138**:350-358 e351.
2. Kabashima K: **New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity.** *J Dermatol Sci* 2013, **70**:3-11.
3. Noda S, Krueger JG, Guttman-Yassky E: **The translational revolution and use of biologics in patients with inflammatory skin diseases.** *J Allergy Clin Immunol* 2015, **135**:324-336.

4. Guttman-Yassky E, Nograles KE, Krueger JG: **Contrasting pathogenesis of atopic dermatitis and psoriasis – part I: clinical and pathologic concepts.** *J Allergy Clin Immunol* 2011, **127**:1110-1118.
5. Guttman-Yassky E, Nograles KE, Krueger JG: **Contrasting pathogenesis of atopic dermatitis and psoriasis – part II: immune cell subsets and therapeutic concepts.** *J Allergy Clin Immunol* 2011, **127**:1420-1432.
6. Brunner PM, Guttman-Yassky E, Leung DY: **The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies.** *J Allergy Clin Immunol* 2017, **139**:S65-S76.
7. Nomura T, Kabashima K, Miyachi Y: **The panoply of alphabetaT cells in the skin.** *J Dermatol Sci* 2014, **76**:3-9.
8. Dainichi T, Hanakawa S, Kabashima K: **Classification of inflammatory skin diseases: a proposal based on the disorders of the three-layered defense systems, barrier, innate immunity and acquired immunity.** *J Dermatol Sci* 2014, **76**:81-89.
9. Nomura T, Kabashima K: **Advances in atopic dermatitis in 2015.** *J Allergy Clin Immunol* 2016, **138**:1548-1555.
10. Honda T, Nomura T, Kabashima K: **Advances in atopic dermatitis and urticaria.** *J Allergy Clin Immunol* 2016.
11. Hamilton JD, Suarez-Farinas M, Dhingra N, Cardinale I, Li X, Kostic A, Ming JE, Radin AR, Krueger JG, Graham N *et al.*: **Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis.** *J Allergy Clin Immunol* 2014, **134**:1293-1300.
12. Khattri S, Shemer A, Rozenblit M, Dhingra N, Czarnowicki T, Finney R, Gilleaudeau P, Sullivan-Whalen M, Zheng X, Xu H *et al.*: **Cyclosporine in patients with atopic dermatitis modulates activated inflammatory pathways and reverses epidermal pathology.** *J Allergy Clin Immunol* 2014, **133**:1626-1634.
13. Tintle S, Shemer A, Suarez-Farinas M, Fujita H, Gilleaudeau P, Sullivan-Whalen M, Johnson-Huang L, Chiricozzi A, Cardinale I, Duan S *et al.*: **Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response.** *J Allergy Clin Immunol* 2011, **128**:583-593 e581-e584.
14. Thaci D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, Soong W, Worm M, Szepletowski JC, Sofen H *et al.*: **Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial.** *Lancet* 2016, **387**:40-52.
15. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E *et al.*: **Dupilumab treatment in adults with moderate-to-severe atopic dermatitis.** *N Engl J Med* 2014, **371**:130-139.
16. Tokura Y: **Extrinsic and intrinsic types of atopic dermatitis.** *J Dermatol Sci* 2010, **58**:1-7.
17. Muraro A, Lemanske RF Jr, Hellings PW, Akdis CA, Bieber T, Casale TB, Jutel M, Ong PY, Poulsen LK, Schmid-Grendelmeier P *et al.*: **Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology.** *J Allergy Clin Immunol* 2016, **137**:1347-1358.
18. Weidinger S, Novak N: **Atopic dermatitis.** *Lancet* 2016, **387**:1109-1122.
19. Czarnowicki T, Esaki H, Gonzalez J, Malajian D, Shemer A, Noda S, Talasila S, Berry A, Gray J, Becker L *et al.*: **Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA) (+) TH2/TH1 cell imbalance, whereas adults acquire CLA(+) TH22/TC22 cell subsets.** *J Allergy Clin Immunol* 2015, **136**:941-951 e943.
- This study reveals multipolarity of cytokine skewing in patients with atopic dermatitis.
20. Rebane A, Zimmermann M, Aab A, Baurecht H, Koreck A, Karelson M, Abram K, Metsalu T, Pihlap M, Meyer N *et al.*: **Mechanisms of IFN-gamma-induced apoptosis of human skin keratinocytes in patients with atopic dermatitis.** *J Allergy Clin Immunol* 2012, **129**:1297-1306.
21. Gittler JK, Shemer A, Suarez-Farinas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, Mitsui H, Cardinale I, de Guzman Strong C, Krueger JG *et al.*: **Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis.** *J Allergy Clin Immunol* 2012, **130**:1344-1354.
- See annotation to Ref. [19**].
22. Akdis CA, Akdis M, Trautmann A, Blaser K: **Immune regulation in atopic dermatitis.** *Curr Opin Immunol* 2000, **12**:641-646.
23. Noda S, Suarez-Farinas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, Peng X, Estrada YD, Nakajima S, Honda T *et al.*: **The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization.** *J Allergy Clin Immunol* 2015, **136**:1254-1264.
- See annotation to Ref. [19**].
24. Ewald DA, Noda S, Oliva M, Litman T, Nakajima S, Li X, Xu H, Workman CT, Scheipers P, Svitacheva N *et al.*: **Major differences between human atopic dermatitis and murine models, as determined by using global transcriptomic profiling.** *J Allergy Clin Immunol* 2017, **139**:562-571.
- This study reveals none of the commonly used murine models for atopic dermatitis fully represents the features of atopic dermatitis in humans. The best murine model that captured characteristics of human atopic dermatitis is IL-23-injected mice, which is considered to mimic human psoriasis vulgaris.
25. Suarez-Farinas M, Dhingra N, Gittler J, Shemer A, Cardinale I, de Guzman Strong C, Krueger JG, Guttman-Yassky E: **Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis.** *J Allergy Clin Immunol* 2013, **132**:361-370.
- See annotation to Ref. [19**].
26. Czarnowicki T, Gonzalez J, Shemer A, Malajian D, Xu H, Zheng X, Khattri S, Gilleaudeau P, Sullivan-Whalen M, Suarez-Farinas M *et al.*: **Severe atopic dermatitis is characterized by selective expansion of circulating TH2/TC2 and TH22/TC22, but not TH17/TC17, cells within the skin-homing T-cell population.** *J Allergy Clin Immunol* 2015, **136**:104-115 e107.
- See annotation to Ref. [19**].
27. Czarnowicki T, Gonzalez J, Bonifacio KM, Shemer A, Xiangyu P, Kunjirava N, Malajian D, Fuentes-Duculan J, Esaki H, Noda S *et al.*: **Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis.** *J Allergy Clin Immunol* 2016, **137**:118-129 e115.
28. Saunders SP, Goh CS, Brown SJ, Palmer CN, Porter RM, Cole C, Campbell LE, Gierlinski M, Barton GJ, Schneider G *et al.*: **Tmem79/Matt is the matted mouse gene and is a predisposing gene for atopic dermatitis in human subjects.** *J Allergy Clin Immunol* 2013, **132**:1121-1129.
29. Moniaga CS, Egawa G, Kawasaki H, Hara-Chikuma M, Honda T, Tanizaki H, Nakajima S, Otsuka A, Matsuoka H, Kubo A *et al.*: **Flaky tail mouse denotes human atopic dermatitis in the steady state and by topical application with *Dermatophagoides pteronyssinus* extract.** *Am J Pathol* 2010, **176**:2385-2393.
30. Oyoshi MK, Beaupre J, Venturelli N, Lewis CN, Iwakura Y, Geha RS: **Filaggrin deficiency promotes the dissemination of cutaneously inoculated vaccinia virus.** *J Allergy Clin Immunol* 2015, **135**:1511-1518 e1516.
31. Oyoshi MK, Murphy GF, Geha RS: **Filaggrin-deficient mice exhibit TH17-dominated skin inflammation and permissiveness to epicutaneous sensitization with protein antigen.** *J Allergy Clin Immunol* 2009, **124**:485-493 e481.
32. Nakajima S, Kitoh A, Egawa G, Natsuaki Y, Nakamizo S, Moniaga CS, Otsuka A, Honda T, Hanakawa S, Amano W *et al.*: **IL-17A as an inducer for Th2 immune responses in murine atopic dermatitis models.** *J Invest Dermatol* 2014, **134**:2122-2130.
- This study indicates multipolarity of cytokines in murine atopic dermatitis model.

33. Saunders SP, Moran T, Floudas A, Wurlod F, Kaszlikowska A, Salimi M, Quinn EM, Oliphant CJ, Nunez G, McManus R *et al.*: **Spontaneous atopic dermatitis is mediated by innate immunity, with the secondary lung inflammation of the atopic march requiring adaptive immunity.** *J Allergy Clin Immunol* 2016, **137**:482-491.
 34. Kawasaki H, Nagao K, Kubo A, Hata T, Shimizu A, Mizuno H, Yamada T, Amagai M: **Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice.** *J Allergy Clin Immunol* 2012, **129**:1538-1546 e1536.
 35. Spergel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS: **Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice.** *J Clin Invest* 1998, **101**:1614-1622.
 36. Spergel JM, Mizoguchi E, Oettgen H, Bhan AK, Geha RS: **Roles of TH1 and TH2 cytokines in a murine model of allergic dermatitis.** *J Clin Invest* 1999, **103**:1103-1111.
 37. Wang G, Savinko T, Wolff H, Dieu-Nosjean MC, Kemeny L, Homey B, Lauerma AI, Alenius H: **Repeated epicutaneous exposures to ovalbumin progressively induce atopic dermatitis-like skin lesions in mice.** *Clin Exp Allergy* 2007, **37**:151-161.
 38. Anthoni M, Wang G, Deng C, Wolff HJ, Lauerma AI, Alenius HT: **Smad3 signal transducer regulates skin inflammation and specific IgE response in murine model of atopic dermatitis.** *J Invest Dermatol* 2007, **127**:1923-1929.
 39. Kaplan DH, Igyarto BZ, Gaspari AA: **Early immune events in the induction of allergic contact dermatitis.** *Nat Rev Immunol* 2012, **12**:114-124.
 40. Allen IC: **Contact hypersensitivity models in mice.** *Methods Mol Biol* 2013, **1032**:139-144.
 41. Kimber I, Dearman RJ: **Allergic contact dermatitis: the cellular effectors.** *Contact Dermatitis* 2002, **46**:1-5.
 42. Kitagaki H, Fujisawa S, Watanabe K, Hayakawa K, Shiohara T: **Immediate-type hypersensitivity response followed by a late reaction is induced by repeated epicutaneous application of contact sensitizing agents in mice.** *J Invest Dermatol* 1995, **105**:749-755.
- This study shows a transition from Th1/Tc1-type to Th2/Tc2-type transition by repeated epicutaneous application of antigens in mice. This finding may partly explain the age dependent differences in cytokine polarities in human AD.
43. Kitagaki H, Ono N, Hayakawa K, Kitazawa T, Watanabe K, Shiohara T: **Repeated elicitation of contact hypersensitivity induces a shift in cutaneous cytokine milieu from a T helper cell type 1 to a T helper cell type 2 profile.** *J Immunol* 1997, **159**:2484-2491.
 44. Kitagaki H, Kimishima M, Teraki Y, Hayakawa J, Hayakawa K, Fujisawa S, Shiohara T: **Distinct in vivo and in vitro cytokine profiles of draining lymph node cells in acute and chronic phases of contact hypersensitivity: importance of a type 2 cytokine-rich cutaneous milieu for the development of an early-type response in the chronic phase.** *J Immunol* 1999, **163**:1265-1273.
 45. Man MQ, Hatano Y, Lee SH, Man M, Chang S, Feingold KR, Leung DY, Holleran W, Uchida Y, Elias PM: **Characterization of a hapten-induced, murine model with multiple features of atopic dermatitis: structural, immunologic, and biochemical changes following single versus multiple oxazolone challenges.** *J Invest Dermatol* 2008, **128**:79-86.
 46. Otsuka A, Doi H, Egawa G, Maekawa A, Fujita T, Nakamizo S, Nakajima C, Nakajima S, Watanabe T, Miyachi Y *et al.*: **Possible new therapeutic strategy to regulate atopic dermatitis through upregulating filaggrin expression.** *J Allergy Clin Immunol* 2014, **133**:139-146 e131-110.
 47. Tanaka A, Matsuda H: **Evaluation of itch by using NC/NgaTnd mice: a model of human atopic dermatitis.** *J Biomed Biotechnol* 2011, **2011**:790436.
 48. Vestergaard C, Yoneyama H, Murai M, Nakamura K, Tamaki K, Terashima Y, Imai T, Yoshie O, Irimura T, Mizutani H *et al.*: **Overproduction of Th2-specific chemokines in NC/Nga mice exhibiting atopic dermatitis-like lesions.** *J Clin Invest* 1999, **104**:1097-1105.
 49. Matsumoto M, Itakura A, Tanaka A, Fujisawa C, Matsuda H: **Inability of IL-12 to down-regulate IgE synthesis due to defective production of IFN-gamma in atopic NC/Nga mice.** *J Immunol* 2001, **167**:5955-5962.
 50. Kohara Y, Tanabe K, Matsuoka K, Kanda N, Matsuda H, Karasuyama H, Yonekawa H: **A major determinant quantitative-trait locus responsible for atopic dermatitis-like skin lesions in NC/Nga mice is located on Chromosome 9.** *Immunogenetics* 2001, **53**:15-21.
 51. Gao XK, Nakamura N, Fuseda K, Tanaka H, Inagaki N, Nagai H: **Establishment of allergic dermatitis in NC/Nga mice as a model for severe atopic dermatitis.** *Biol Pharm Bull* 2004, **27**:1376-1381.
 52. Walter MR, Windsor WT, Nagabhushan TL, Lundell DJ, Lunn CA, Zauodny PJ, Narula SK: **Crystal structure of a complex between interferon-gamma and its soluble high-affinity receptor.** *Nature* 1995, **376**:230-235.
 53. Kraich M, Klein M, Patino E, Harrer H, Nickel J, Sebald W, Mueller TD: **A modular interface of IL-4 allows for scalable affinity without affecting specificity for the IL-4 receptor.** *BMC Biol* 2006, **4**:13.
 54. Lowes MA, Suarez-Farinas M, Krueger JG: **Immunology of psoriasis.** *Annu Rev Immunol* 2014, **32**:227-255.
 55. Amin M, Darji K, No DJ, Wu JJ: **Review of phase III trial data on IL-23 Inhibitors Tildrakizumab and Guselkumab for psoriasis.** *J Eur Acad Dermatol Venereol* 2017.
 56. Schon MP: **Animal models of psoriasis: a critical appraisal.** *Exp Dermatol* 2008, **17**:703-712.
 57. Nickoloff BJ: **Keratinocytes regain momentum as instigators of cutaneous inflammation.** *Trends Mol Med* 2006, **12**:102-106.
 58. Schon MP: **Animal models of psoriasis – what can we learn from them?** *J Invest Dermatol* 1999, **112**:405-410.
 59. Schlapbach C, Gehad A, Yang C, Watanabe R, Guenova E, Teague JE, Campbell L, Yawalkar N, Kupper TS, Clark RA: **Human TH9 cells are skin-tropic and have autocrine and paracrine proinflammatory capacity.** *Sci Transl Med* 2014, **6**:219ra218.
 60. Wolfram JA, Diaconu D, Hatala DA, Rastegar J, Knutsen DA, Lowther A, Askew D, Gilliam AC, McCormick TS, Ward NL: **Keratinocyte but not endothelial cell-specific overexpression of Tie2 leads to the development of psoriasis.** *Am J Pathol* 2009, **174**:1443-1458.
 61. van der Fits L, Mourits S, Voerman JS, Kant M, Boon L, Laman JD, Cornelissen F, Mus AM, Florencia E, Prens EP *et al.*: **Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis.** *J Immunol* 2009, **182**:5836-5845.
 62. Swindell WR, Johnston A, Carbajal S, Han G, Wohn C, Lu J, Xing X, Nair RP, Voorhees JJ, Elder JT *et al.*: **Genome-wide expression profiling of five mouse models identifies similarities and differences with human psoriasis.** *PLOS ONE* 2011, **6**:e18266.
- This study summarizes the variabilities in the murine models of psoriasis in comparison with human psoriasis in terms of genome-wide gene expression profile.
63. Vinter H, Kragballe K, Steiniche T, Gaestel M, Iversen L, Johansen C: **Tumour necrosis factor-alpha plays a significant role in the Aldara-induced skin inflammation in mice.** *Br J Dermatol* 2016, **174**:1011-1021.
 64. Cook PW, Piepkorn M, Clegg CH, Plowman GD, DeMay JM, Brown JR, Pittelkow MR: **Transgenic expression of the human amphiregulin gene induces a psoriasis-like phenotype.** *J Clin Invest* 1997, **100**:2286-2294.
 65. Cook PW, Brown JR, Cornell KA, Pittelkow MR: **Suprabasal expression of human amphiregulin in the epidermis of transgenic mice induces a severe, early-onset, psoriasis-like skin pathology: expression of amphiregulin in the basal**

- epidermis is also associated with synovitis. *Exp Dermatol* 2004, **13**:347-356.
66. Sano S, Chan KS, Carbajal S, Clifford J, Peavey M, Kiguchi K, Itami S, Nickoloff BJ, DiGiovanni J: **Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model.** *Nat Med* 2005, **11**:43-49.
67. Sato K, Takaishi M, Tokuoka S, Sano S: **Involvement of TNF-alpha converting enzyme in the development of psoriasis-like lesions in a mouse model.** *PLOS ONE* 2014, **9**: e112408.
68. Nakajima K, Kanda T, Takaishi M, Shiga T, Miyoshi K, Nakajima H, Kamijima R, Tarutani M, Benson JM, Elloso MM *et al.*: **Distinct roles of IL-23 and IL-17 in the development of psoriasis-like lesions in a mouse model.** *J Immunol* 2011, **186**:4481-4489.
69. Li AG, Wang D, Feng XH, Wang XJ: **Latent TGFbeta1 overexpression in keratinocytes results in a severe psoriasis-like skin disorder.** *EMBO J* 2004, **23**:1770-1781.
70. Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S, Lucian L, Geissler R, Brodie S, Kimball AB *et al.*: **IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis.** *J Exp Med* 2006, **203**:2577-2587.
71. Rizzo HL, Kagami S, Phillips KG, Kurtz SE, Jacques SL, Blauvelt A: **IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17A.** *J Immunol* 2011, **186**:1495-1502.
72. Lindroos J, Svensson L, Norsgaard H, Lovato P, Moller K, Hagedorn PH, Olsen GM, Labuda T: **IL-23-mediated epidermal hyperplasia is dependent on IL-6.** *J Invest Dermatol* 2011, **131**:1110-1118.