REVIEW ARTICLE
https://doi.org/10.1038/s41590-018-0256-2

nature immunology

The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis

Teruki Dainichi[1*], Akihiko Kitoh[1], Atsushi Otsuka[1], Saeko Nakajima[1], Takashi Nomura[1], Daniel H. Kaplan[2] and Kenji Kabashima[1,3*]

The skin provides both a physical barrier and an immunologic barrier to external threats. The protective machinery of the skin has evolved to provide situation-specific responses to eliminate pathogens and to provide protection against physical dangers. Dysregulation of this machinery can give rise to the initiation and propagation of inflammatory loops in the epithelial microenvironment that result in inflammatory skin diseases in susceptible people. A defective barrier and microbial dysbiosis drive an interleukin 4 (IL-4) loop that underlies atopic dermatitis, while in psoriasis, disordered keratinocyte signaling and predisposition to type 17 responses drive a pathogenic IL-17 loop. Here we discuss the pathogenesis of atopic dermatitis and psoriasis in terms of the epithelial immune microenvironment—the microbiota, keratinocytes and sensory nerves—and the resulting inflammatory loops.

The skin functions as both a physical barrier and an immunological organ that has evolved to defend living organisms against pathogens and physical dangers, as well as to maintain tissue homeostasis. The skin is composed of the epidermis, dermis (including papillary and reticular dermis) and subcutaneous fat (Fig. 1a). The epidermis is the outer layer, which forms the barrier via the stratum corneum and tight junctions. The uppermost layer of the dermis just beneath the epidermis, composed of fine collagen bundles with plentiful perfusion and innervation, is the papillary dermis. The epidermis and the papillary dermis take part in the immunological microenvironment mainly at the very superficial sites of the skin around 0.1–0.2 mm from the body surface (Fig. 1a). A wide variety of protective and pathogenic immune responses can be induced in the skin by an array of skin-resident and skin-infiltrating immune cells of both the innate immune system and adaptive immune system[1]. In addition, non-immune skin components, such as keratinocytes, have a substantial role in the recruitment and activation of immune cells in the inflamed skin via the elaboration of soluble mediators (Fig. 1b). Cytokines produced by immune cells in the inflamed skin affect the proliferation and activation of non-immune cells, which generates a complex inflammatory network, especially during chronic skin inflammation.

The protective machinery of the body opposes external agents (such as poisons, mites, worms and fungi) in the skin by barrier and innate and adaptive immunity that appropriately eliminate each opponent (Fig. 1c). Type 2 responses are elicited to remove mites and poisons at the body surface by inducing scratching. Type 17 responses attempt to exclude dermatophytes (such as *Trichophyton* and *Candida* species) by accelerating exfoliation of the stratum corneum and recruiting neutrophils that suppress the proliferation of dermatophytes. Dysregulation of the protective machinery of the skin can give rise to various types of inflammatory skin diseases that simulate such originally defensive reactions. Atopic dermatitis (AD) and psoriasis are common chronic inflammatory skin diseases that are mediated by immune cells, in particular, T cells[2–7]. Accordingly, biologics that target T cell effector cytokines and receptors, such as interleukin 17A (IL-17A; called simply 'IL-17' here) for psoriasis and the cytokine receptor subunit IL-4Rα for AD, are clinically highly effective. Less well defined, however, is how the local interplay among activated immune cells, keratinocytes, peripheral nerves and the skin microbiota contributes to the specific inflammatory context that results in the pathogenesis of AD and psoriasis.

Thus, the current understanding of protective and pathological immune responses of the skin suggests that skin immune responses are determined and organized largely at the epithelial immune microenvironment (EIME) in the epidermis and papillary dermis at the very surface of the skin (Fig. 1a). The epidermis contributes to host defense by barrier formation, the release of soluble mediators and direct sensing of external agents (Fig. 1b) while the papillary dermis is where immune cells and non-immune components interact. Furthermore, the microbiota and peripheral nerves should also be the important components of the EIME. Here we review the functions of cutaneous immunological mediators on the basis of clinical studies of AD and psoriasis and consider how the EIME generates and perpetuates pathogenic inflammatory loops.

Pathogenesis of AD

AD is clinically characterized by chronic, pruritic eczematous skin lesions[8,9] and is accompanied by elevated serum concentrations of immunoglobulin E (IgE)[9]. The disease prevalence of AD has two age peaks: in infancy and in the third decade of life (20–29 years of age). AD in infancy is mostly spontaneously ameliorated by adolescence[10] (Fig. 2a). T_H2-type inflammation is considered to be essential for the pathogenesis of AD[8]. Published studies have shown that blockade of IL-4Rα, which composes the receptor for both IL-4 and IL-13, is highly effective for the treatment of AD[11], indicative of a substantial role for signaling via IL-4 and IL-13 in the pathogenesis of AD. T_H2 cells are the main source of IL-4 and IL-13 in AD, but basophils and group 2 innate lymphoid cells (ILC2s) are also potential sources[12]. During disease initiation, IL-4 and IL-13 induce the differentiation and activation of T_H2 cells and also induce immunoglobulin class switching to IgE[13]. Barrier dysfunction due

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan. [2]Department of Dermatology and Department of Immunology, Cutaneous Biology Research Core, University of Pittsburgh, Pittsburgh, PA, USA. [3]Singapore Immunology Network (SIgN) and Institute of Medical Biology, Agency for Science, Technology and Research (A*STAR), Biopolis, Singapore, Singapore. *e-mail: dainichi@kuhp.kyoto-u.ac.jp; kaba@kuhp.kyoto-u.ac.jp

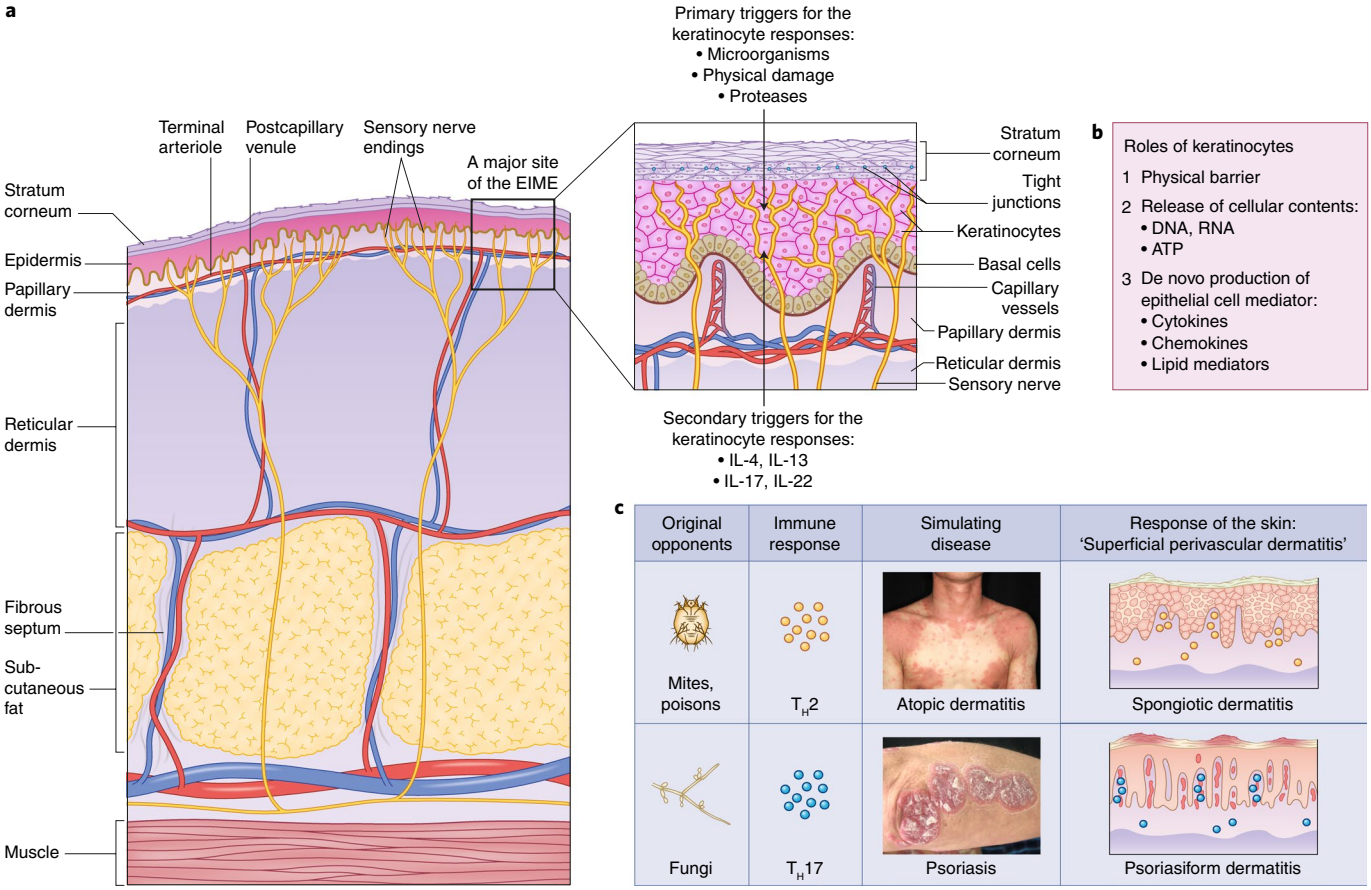


Fig. 1 | Skin as a protective organ. a, The skin is composed of the epidermis, dermis and subcutaneous fat. The stratum corneum is the outermost layer of the epidermis. The dermis is subdivided into the papillary dermis immediately beneath the epidermis, and the reticular dermis. The papillary dermis is composed of fine collagen bundles and is perfused with blood vessels (terminal arterioles, capillary vessels and postcapillary venules) and sensory nerve endings, whereas the reticular dermis is composed of thick collagen bundles and mainly governs the solid architecture of the skin. In both AD and psoriasis, most inflammatory events are located in the epidermis and papillary dermis that organize the EIME of these diseases, at a depth of 0.1–0.2 mm from the body surface. The epidermis contributes to the EIME in two phases. First, keratinocytes compose the outermost defense system of the body as a barrier, sensor and responder mainly for external agents (listed in **b**). Second, keratinocytes are the amplifier of immune responses at the EIME; the cytokine products of type 2 or type17 inflammation further elicit keratinocyte activation that enhances each type of inflammation. **b**, Three layers of roles for keratinocytes in the immune response of the skin. **c**, Types of superficial perivascular dermatitis. The skin opposes harmful agents at the body surface by the most appropriate responses. For insects and poisons, the epidermis is prepared to be removed together with these external substances via the induction of scratching behavior though T_H2 responses, which is histologically called 'spongiotic dermatitis'. For fungi at the body surface, the skin removes them together with the stratum corneum by accelerating its turnover and the infiltration of neutrophils, mediated by the T_H17 response, which is called 'psoriasiform dermatitis'. These responses are simulated in part by several noninfectious inflammatory skin diseases and are sometimes indistinguishable without the detection of pathogens[1].

to impaired terminal differentiation of keratinocytes is thought to allow increased penetration of cutaneous antigens that results in the initiation of AD[14]. In addition, chronic itching and subsequent dysbiosis with predominant colonization by *Staphylococcus aureus* are considered essential for the maintenance of AD. Thus, clinical evidence suggests that IL-4 and IL-13 serve a central role in the chronicity of AD by driving a type 2 inflammation loop (Fig. 3a) that is discussed in detail below.

Clinical studies have suggested that the other type 2 mediators, such as IL-5 and IgE, are less important for AD pathogenesis. This is probably because they do not drive the type 2 inflammatory loop. For example, administration of a monoclonal IL-5 antagonist to patients with AD reduced peripheral eosinophilia but did not sufficiently ameliorate disease, although the results of a phase 2 study of AD with eosinophilia have not been published[15,16]. The efficacy of a monoclonal antibody to IgE that inhibits the binding of free IgE to its receptor FcεRI in patients with AD remains controversial because omalizumab and ligelizumab, which are biologics directed against IgE, have not shown clinical efficacy in AD, whereas their possible efficacy in children and severe AD is now being explored[16]. IL-22 is a type 17 cytokine, but the results of clinical trials of an antibody to IL-22 in AD suggest that IL-22 has a pathogenic role in severe cases of AD[17].

Pathogenesis of psoriasis

Psoriasis is a common chronic inflammatory skin disease that is clinically characterized by red scaly papules and plaques with a prevalence generally estimated at 1–3% of the population worldwide[18,19]. Histologically, there is considerable thickening of the epidermis due to an increased proliferation of keratinocytes with a dense dermal infiltrate of immune cells, such as T cells and dendritic cells (DCs). Clinical studies of selective biologics that target the immune system have demonstrated that the cytokines TNF (tumor-necrosis factor), IL-23 and IL-17 have a pivotal role in the pathogenesis

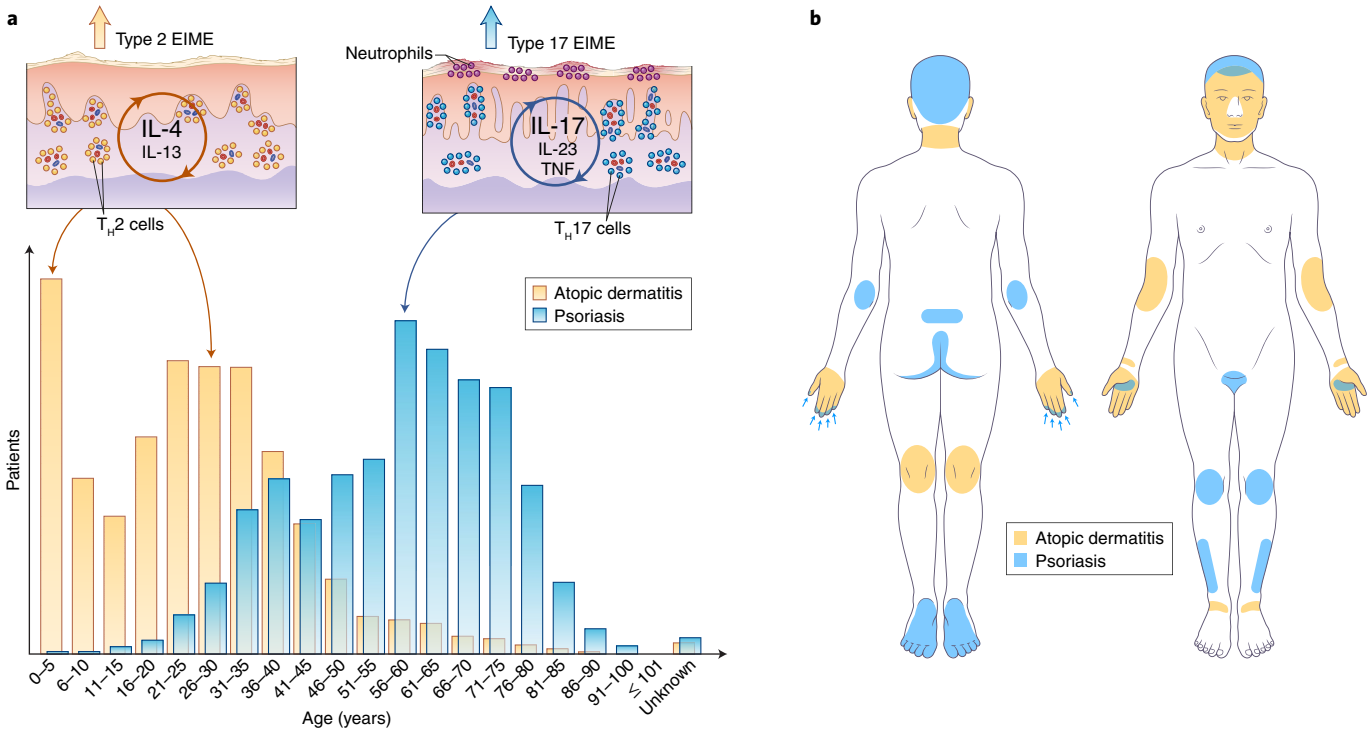


Fig. 2 | Age distribution and sites of predilection in AD and psoriasis. a, Age distribution of AD and psoriasis (key), based upon a study done in outpatient clinics in Japan in 2007–2008[10] (bottom). AD has two age peaks (infancy and the third decade of life) in disease prevalence and is spontaneously ameliorated, whereas psoriasis develops in the fourth decade of life (30–39 years of age) or later in most cases and is intractable without treatment. The results of cytokine-blockade therapies have led to the conclusion that very few cytokines are critical to AD or psoriasis (top). Blockade of IL-4 or IL-13 significantly reduces AD inflammation. Blockade of IL-17, IL-23 or TNF results in almost complete recovery from psoriasis. Both AD and psoriasis are histopathologically classified as 'superficial perivascular dermatitis', in which most of the infiltration by inflammatory cells is restricted to the very superficial region of the dermis and part in the epidermis, where the EIME is composed. This EIME is therefore expected to be a major site of the production of these cytokines, which suggests that each plot (bottom) also tracks the magnitude of the type 2 or type 17 EIME in each disease course at the very surface of the skin. **b**, Predilection sites for AD and psoriasis (key). The involvement of AD at the cubital and popliteal fossae is identical to the sites of predominant colonization with *S. aureus*. The center of the face is usually spared. In psoriasis, Koebner phenomenon (the development of skin lesions at the physiologically stressed sites) is very evident and results in predilection for psoriasis at the flexor sides of extremities, sacral region and soles of the feet. Scalp and nails are also predilection sites in psoriasis.

of psoriasis, whereas other long-suspected participants, such as interferon-γ (IFN-γ) and IL-1β, do not[20].

The efficacy of TNF inhibitors for psoriasis has demonstrated the essential action of TNF in psoriasis[20]. The inflammatory events in psoriasis are characterized by the activation of TNF and inducible nitric oxide synthase–producing DCs (Tip-DCs)[21–25], which produce TNF and IL-23 and subsequently induce type 17 inflammation. One of the multifaceted effects of TNF inhibition is blockade of the autocrine–paracrine loop of TNF by Tip-DCs. Consistent with that, neutralization of TNF induces rapid downregulation of maturation markers on cutaneous DCs as well as downregulation of DC products, including both IL-23 subunits (p19 and p40)[23]. TNF might also contribute to the development of psoriatic dermatitis through the activation of keratinocytes: TNF and IL-17 synergistically stimulate keratinocytes to fully produce key inflammatory molecules in psoriasis, such as CCL20 and IL-8. These results are in consistent with the efficacy of psoriasis therapy through the blockade of either TNF or IL-17[26].

Selective inhibition of either subunit of IL-23 (p19 or p40) has great efficacy in the treatment of psoriasis[27]. This is consistent with the results of blockade of IL-17, because IL-23 is considered to be essential for the maintenance and activation of the T_H17 subset of helper T cells[28].

Blockade of IL-17 signaling through the use of monoclonal antibodies to IL-17 or its receptor has ameliorated psoriatic lesions drastically, with reduced proliferation of keratinocytes, infiltration of T cells into the skin and expression of mRNA from key psoriasis-associated genes[29–32]. In addition to $CD4^+$ or $CD8^+$ αβ T cells and dermal γδ T cells, mast cells, neutrophils and ILC3s are known to be cellular sources of IL-17 in psoriasis[33–35]. Despite the known role of another T_H17 cytokine, IL-22, in psoriasis through its induction of keratinocyte proliferation, antimicrobial peptide production and neutrophil recruitment[36], IL-22-blockade therapies have not shown any definitive efficacy for psoriasis[37], unlike their efficacy in AD[17], which suggests that IL-22 might have a less pathogenic role in psoriasis. IL-27 is known to promote T_H1 responses but inhibits T_H17 responses, but its protective role in psoriatic inflammation remains controversial because two independent studies of IL-27 blockade in imiquimod-induced psoriatic inflammation have reported conflicting results[38,39]. It remains to be elucidated exactly how IL-17 promotes a complex inflammatory condition in the lesional skin of psoriasis.

Thus, a series of clinical studies have identified a definitive contribution of the IL-23–IL-17 axis to the development and maintenance of psoriatic inflammation, as well as its dependence on TNF.

Pathogenic features from comorbidities and genomic studies

AD generally develops in infancy and or during the third decade of life (Fig. 2a). AD is frequently followed by the comorbidities of other T_H2 cell–mediated allergic diseases, such as asthma and food

allergies, called the 'atopic–allergic march'[40]. However, the prevalence of comorbidities in AD is not determined only by intrinsic immunological characteristics. Genome-wide association studies (GWASs) have demonstrated that epithelial factors also contribute to the pathogenesis of AD and its complication with other allergic diseases (Table 1).

Published studies have indicated that AD shares with asthma various disease-risk single-nucleotide polymorphisms (SNPs) in T_H2 cell–related genes, such as *Il13*[41,42], which suggests that an intrinsic predisposition to T_H2 responses is critical for the association of T_H2 cell–related diseases. On the other hand, however, identification of a link between nonsense mutations in *FLG*, which encodes filaggrin, a barrier protein of the skin, and the incidence of AD[43] and even asthma[44] has established a new paradigm that skin-barrier defects give rise to the deviation to T_H2 responses in the skin and subsequent coexistence of T_H2 cell–related diseases in other organs, such as the lungs. Further recent GWASs have identified additional AD-associated loci in *C11orf30* that are also associated with epithelial autoimmune diseases and epithelium-derived cancers[45], and *OVOL1* and *LCE3A*, which encode molecules that regulate barrier formation of the skin[46,47]. Other risk loci shared by AD and asthma include multiple genes that encode the components of the cytokine receptors IL-33R and IL-18R[48,49] (Table 1). These findings suggest that comorbidities of atopic diseases are determined largely by epithelial predisposition beyond a predisposition to T_H2 responses[50,51].

Psoriasis develops in middle age, usually becomes chronic (Fig. 2a) and is commonly associated with a metabolic syndrome (such as obesity, hyperlipidemia or atherosclerosis). In marked contrast to the frequent coexistence of T_H2 cell–related diseases in AD, however, psoriasis is not commonly associated with other T_H17 cell–related diseases (such as rheumatoid arthritis)[52]. Although psoriasis can be associated with arthritis (psoriatic arthritis), the latter is considered not an independent T_H17 cell–related disease but a complication of psoriasis. Other chronic inflammatory diseases that are sensitive to therapies directed against TNF (such as rheumatoid arthritis, inflammatory bowel disease and Behçet's disease) share the comorbidities of metabolic syndrome[53–55], suggestive of a link between chronic inflammation and metabolic syndrome. In contrast to the 'atopic march' among T_H2 cell–related diseases that share a barrier disorder, however, diseases sensitive to antibodies to TNF (anti-TNF) that share the metabolic risk are not usually complicated with other diseases sensitive to anti-TNF. Thus, the association of metabolic syndrome with psoriasis might be a consequence, rather than a cause, of TNF-driven inflammation, although the precise mechanisms of the association between psoriasis and metabolic syndrome remain under debate.

Whereas GWASs have demonstrated a genetic predisposition to T_H17 responses in patients with psoriasis (Table 1), the identification of gene mutations in familial-type psoriasis has suggested a unique role for keratinocyte signaling in the development of psoriasis that has not been indicated in studies of other T_H17 cell–related diseases, such as rheumatoid arthritis. The caspase-recruitment domain CARD14 is expressed predominantly in the epidermis, and gain-of-function mutations in *CARD14* are found in familial-type psoriasis[56]. CARD14 is supposed to form signalosomes and activate the transcription factor NF-κB and the mitogen-activated protein kinases (MAPKs) p38 and JNK. Mutations in *IL36RN*, which encodes the antagonist for IL-36R, a receptor for cytokines of the IL-1 family that is expressed selectively in keratinocytes, are found in generalized pustular psoriasis[57]. Furthermore, several genes encoding the regulators of these pathways, such as A20 (*TNFAIB3*), IκBα (*NFKBIA*), ABIN-1 (A20-binding and inhibitor of NF-κB 1) (*TNIP1*) and IκBζ (*NFKBIZ*), have been identified in psoriasis-susceptibility loci by GWASs[18,58] (Table 1).

Thus, genetic evidence suggests that epithelial factors have important roles in the development of AD and its T_H2 cell–related comorbidities, while a predisposition to T_H17 responses and dysregulation of inflammatory signaling in immune and non-immune components, such as keratinocytes, contribute to the development of psoriasis. Clinical and experimental evidence therefore indicates that the inflammatory loop at the EIME determines the key features of AD and psoriasis. We describe the details of the inflammatory loop at the EIME in each disease in the following sections.

The inflammatory loop in AD

External agents stimulate skin-resident DCs or other immune cells to induce their production of inflammatory cytokines, which activate keratinocytes[59–61]. Conversely, external agents can also directly induce keratinocyte responses that affect subsequent inflammatory events[34,62–64]. These keratinocyte responses are considered to trigger development of the EIME in both atopic inflammation and psoriatic inflammation and the subsequent propagation and chronicity of the disease at the interface of the body and the external environment. Barrier impairment is critical for keratinocyte responses, dysbiosis of the skin and pruritus, and the consequent scratching behavior accelerates damage to the skin barrier.

The master initiator of the type 2 inflammation in the skin, lungs and gut remains controversial despite several proposals, including basophils[65], DCs[66,67], ILC2s[68,69] and epithelial cells[69,70]. The present understanding, however, suggests all of the candidates above are involved in the induction of type 2 inflammation. In response to allergens, proteases, crystals and infectious agents, epithelial cells release epithelial type 2 mediator cytokines, such as TSLP (thymic stromal lymphopoietin), IL-33, GM-CSF and IL-25[61,71,72]. These epithelial cytokines activate basophils, ILC2s, and DCs in the skin and induce the production of T_H2 cytokines. These T_H2 cytokines directly drive the epithelial cells to further produce epithelial

Fig. 3 | Theoretical inflammatory loops at the EIME. a, Theoretical inflammatory loops of AD (left) and psoriasis (right). Keratinocytes have pivotal roles in driving the inflammatory loop of type 2 inflammation in AD and that of type 17 inflammation in psoriasis. Although both the microbiota and the sensory nerves contribute to disease propagation by driving each loop through barrier dysfunction and keratinocyte activation in AD, their contribution remains obscure in psoriasis. **b**, The inflammatory loop of the skin microbiota. Diverse microbes (viruses, fungi and bacteria) cover skin surface of healthy skin with an intact barrier. AD skin, in line with barrier dysfunction, exhibits low microbial diversity, which is 'dysbiosis'. AD skin is heavily colonized by *S. aureus*. Barrier dysfunction leads to changes in the skin environment, which might have an important role in the development of *S. aureus* colonization. The colonization of mouse skin by *S. aureus* directly induces serine-protease activity that disrupts the epidermal barrier. *S. aureus*–derived δ-toxin induces mast-cell degranulation, which might contribute to disease flare and itching. The inflammatory loop of the skin microbiota must drive through the barrier impairment or keratinocyte responses. **c**, The inflammatory loop of sensory nerves and pruritus. Under the barrier impairment in AD, damaged keratinocytes produce cytokines such as TSLP, IL-25 and IL-33. These cytokines stimulate ILC2s. The responding ILC2s promptly produce IL-5 that activates eosinophils, and IL-13 that activates T_H2 cells. IL-4, IL-13 and IL-31 directly activate sensory nerves, which promotes pruritus. TLSP and artemin from keratinocytes also directly stimulate sensory nerves. Sensory nerves modulate the dermal DCs to activate the IL-23–IL-17 axis. The inflammatory loop of sensory nerves is completed only in type 2 responses through the pruritus and scratching behavior that causes the barrier impairment and keratinocyte responses. Direct roles for peripheral nerves in the induction of the T_H2 response have been demonstrated in animal gut and lungs[141] but not in the skin. PAMP, pathogen-associated molecular pattern.

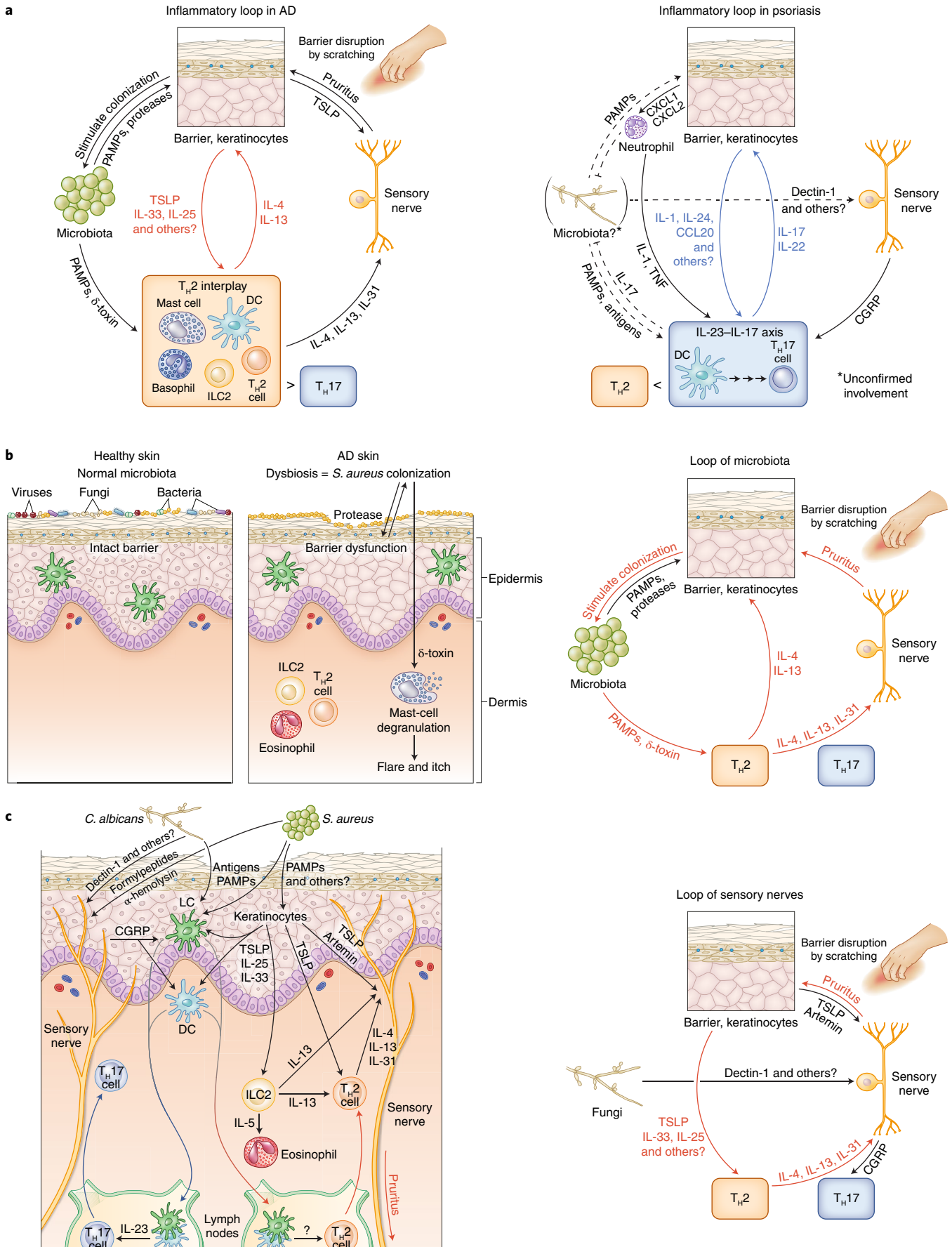

a
Inflammatory loop in AD
Barrier disruption by scratching
Pruritus
TSLP
Stimulate colonization
PAMPs, proteases
Barrier, keratinocytes
Microbiota
TSLP
IL-33, IL-25
and others?
IL-4
IL-13
Sensory nerve
PAMPs, δ-toxin
TH2 interplay
Mast cell
DC
Basophil
ILC2
TH2 cell
IL-4, IL-13, IL-31
>
TH17
Inflammatory loop in psoriasis
PAMPs
CXCL1
CXCL2
Neutrophil
Barrier, keratinocytes
Microbiota?*
Dectin-1
and others?
Sensory nerve
IL-1, IL-24,
CCL20
and
others?
IL-17
IL-22
IL-1, TNF
IL-17
PAMPs, antigens
CGRP
IL-23–IL-17 axis
DC
TH17 cell
TH2
<
*Unconfirmed involvement
b
Healthy skin
Normal microbiota
Viruses
Fungi
Bacteria
Intact barrier
AD skin
Dysbiosis = S. aureus colonization
Protease
Barrier dysfunction
Epidermis
Dermis
δ-toxin
ILC2
TH2 cell
Eosinophil
Mast-cell degranulation
Flare and itch
Loop of microbiota
Barrier disruption by scratching
Pruritus
Stimulate colonization
PAMPs, proteases
Barrier, keratinocytes
Sensory nerve
Microbiota
IL-4
IL-13
PAMPs, δ-toxin
IL-4, IL-13, IL-31
TH2
TH17
c
C. albicans
S. aureus
Dectin-1 and others?
Formylpeptides
α-hemolysin
Antigens
PAMPs
PAMPs
and others?
LC
Keratinocytes
CGRP
TSLP
IL-25
IL-33
TSLP
TSLP
Artemin
Sensory nerve
DC
IL-13
IL-4
IL-13
IL-31
TH17 cell
ILC2
IL-13
TH2 cell
IL-5
Eosinophil
Sensory nerve
Pruritus
IL-23
Lymph nodes
?
TH2 cell
TH17 cell
Loop of sensory nerves
Barrier disruption by scratching
Pruritus
TSLP
Artemin
Barrier, keratinocytes
Dectin-1 and others?
Sensory nerve
Fungi
TSLP
IL-33, IL-25
and others?
IL-4, IL-13, IL-31
CGRP
TH2
TH17

Table 1 | Genetic susceptibility loci of AD and psoriasis

Category	AD[43–51]		Psoriasis[18,150]
	Shared in atopic diseases		
HLA and its processing		*B44*, *B57*, *DQA02*, *DQA03*, *DQB02*, *DQB03*, *DRB04*, *DRB07*, ***GPSM3***	*HLA-A*, *HLA-B*, *HLA-C12*, *HLA-DQA1*, *ERAP1*
NF-κB signaling	***TNFRSF6B*–*ZGPAT***	***NALP10***, ***CARD11***	*REL*, *TNIP1*, *NFKBIA*, *CARD14*, *IFIH1*, *DDX58*, *RNF114*
JAK signaling	*IL6R*		*IL28RA*, *TYK2*
TGF-β signaling	*SMAD3*		
T-cell regulation	*IL2*-*IL21*	*LRRC32*, ***ZNF365*–*EGR2***	*RUNX3*, *TAGAP*, *ETS1*, *MBD2*, *PTPN22*
IL-23–IL-17 axis			*TNFAIP3*, *IL23R*, *IL12B*, *TRAF3IP2*, *IL23A*, *STAT3*
T_H2	***KIF3A*–*IL13*, *IL1RL1*–*IL18R1*–*IL18RAP*–*SLC9A4***	***GLB1*–*CCR4***	*IL4*, *IL13*
Barrier	***FLG***, ***OVOL1***	*LCE3A*	*LCE3B*, *LCE3C*, *LCE3D*
Epithelium	***C11orf30***, ***TNFRSF6B*–*ZGPAT***, *GSDMA*, *GSDMB*	***CCDC80***, *ZNF652*	*CARD14*
Mitochondria	***TMEM232*–*SLC25A46***	***CYP24A1*–*PFDN4***	
Apoptosis		*PRR5L*	
Autophagy		*CLEC16A*–*DEXI*	
Unknown		***ACTL9***	*CDKAL1*

Bold plus underlining indicates loci shared by European and Asian people; underlining indicates European loci; bold indicates Asian loci, for AD-susceptibility loci. The ethnicity of psoriasis-susceptible loci is not indicated.

type 2 mediators via their receptors, which completes the loop of type 2 inflammation. Thus, interplay between the epidermis and the organization of type 2 immune cells (including basophils, mast cells, ILC2s, DCs and T_H2 cells) is considered to drive the type 2 inflammatory loop in AD (Fig. 3a). Despite progress in this field, the mechanism that initiates and propagates the epithelial cell responses that is unique to AD remains obscure.

The inflammatory loop in psoriasis

Activation of the IL-23–IL-17 axis predominantly in the skin defines psoriatic inflammation[59,73] and distinguishes this disorder from AD or other type 17 response–mediated inflammatory disorders that affect other organs[74].

Activation of the IL-23–IL-17 axis is believed to be initiated by the activation of skin-resident DCs and their production of IL-23 that drives T cells to produce type 17 cytokines, such as IL-17 and IL-22. IL-17 activates epidermal keratinocytes via IL-17R to produce proinflammatory cytokines and chemokines, such as IL-1, IL-6, CXCL1 (C-X-C motif ligand) and CCL20 (C-C motif ligand 20), which are known to induce and propagate psoriatic inflammation[19]. In other contexts, IL-23 drives the production of IL-22 by ILC3s and might also drive a local skin inflammatory loop, in addition to the maintenance of T_H17 cells[34]. IL-22 induces epidermal hyperplasia independently of IL-17, which suggests that it has diverse roles and illustrates the redundancy of the type 17 cytokines[75]. However, the lesser effect of IL-22-blockade therapies in psoriasis than in AD suggests that IL-22 is not an essential participant in the type 17 inflammatory loop in psoriasis[37].

It has long been suggested that the epidermis provides a 'cue' for the activation of skin-resident DCs in psoriasis[19], and it has been demonstrated in mice that the epidermis has an essential role in psoriatic inflammation[76]. Notably, cutaneous administration of IL-23 is not sufficient to induce psoriatic inflammation in germ-free mice[77], indicative of an additional role for the skin microbiota. Whereas penetration through tight junctions by dendrites of Langerhans cells (LCs) that sense the skin microbiota is evident in AD, compared with healthy donors, this feature of LCs is not substantial in psoriasis lesional skin[78] despite the potential involvement of LCs in psoriatic inflammation[79]. So far, abnormalities in the skin microbiota have not been well demonstrated in psoriasis, and involvement of the skin microbiota in the inflammatory loop of psoriasis is an issue that remains to be solved, as discussed below. The positive feedback loop of type 17 cytokines to sensory nerves remains unclear.

Thus, the interplay between the IL-23–IL-17 axis and keratinocytes is central to the IL-17-mediated inflammatory loop in psoriasis (Fig. 3a). Despite the definitive role of keratinocytes in this loop, the complete pathway between the IL-23–IL-17 axis and the other components of the EIME (such as the microbiota and sensory nerves) has not yet been demonstrated (Fig. 3b,c), and the precise features of these elements in driving the IL-17 inflammatory loop in psoriasis remain to be elucidated.

The microbiota of the skin in AD and psoriasis

S. aureus has long been known as a key participant in the pathogenesis of AD. Studies of the microbiota of the skin have demonstrated the contribution of commensal bacteria to the immunological homeostasis of the skin as well as that of the gut and the relationship among skin microbial imbalance, 'dysbiosis' and the development of inflammatory skin diseases[80]. Skin dysbiosis can be directly sensed by the immune system. In addition, it has been suggested that dysbiosis directly affects other participants in the skin: propagation of *S aureus* colonization gives rise to protease-mediated barrier disruption[81]; dysbiosis causes a change in the composition of pathogen-associated molecular patterns that is sensed by keratinocytes through a series of pattern-recognition receptors[82]; and *Candida albicans* activates $TRPV1^+$ sensory nerves[83]. Dysbiosis is therefore involved in the subsequent inflammatory loop of the skin, particularly in AD, regardless of its being a cause or a consequence.

Gene-sequencing studies of 16S ribosomal RNA have clearly demonstrated the predominant colonization with *S. aureus* in healthy skin at the sites at which patients with AD are commonly

affected[84] (Fig. 2b). Consistent with that, the skin microbiome of patients with AD has decreased bacterial diversity and increased predominance of colonization with *S. aureus*[85], and specific strains of *S. aureus* are associated with more-severe AD[86]. How *S. aureus* in the skin is involved in the pathogenesis of AD has been proposed by animal studies. Serine proteases from *S. aureus* are involved in barrier disruption and type 2 inflammation[81]. *S. aureus* δ-toxin induces the degranulation of dermal mast cells and subsequent type 2 responses and skin desquamation[60] (Fig. 3b).

Although some studies have suggested a potential contribution of the skin microbiota to psoriasis[87–89], clear evidence that dysbiosis is critical to psoriatic inflammation has not been identified. The skin microbiota from psoriasitic lesions show compositions of skin-associated genera (*Corynebacterium*, *Propionibacterium*, *Staphylococcus* and *Streptococcus*) genetically similar to those of unaffected or healthy skin[90,91]. The fungal microbiota in the psoriasitic lesional skin also seems to be similar to that of nonlesional or healthy skin[92,93].

Thus far, it has been well demonstrated that the interaction of the microbiota at the EIME contributes to the development of a loop of type 2 inflammation in AD, but this not yet been shown for type 17 inflammation in psoriasis (Fig. 3b).

Barriers in AD and psoriasis

Keratinocytes have three layers of roles as a barrier, in the release cellular contents and in the de novo production of epithelial cell mediators (Fig. 1b). The stratum corneum governs mainly the physiological barrier of the skin[40]. Epithelial cell–cell contact, including tight junctions at the stratum granulosum, also contributes to this function, and defects in either can be related to the T_H2 response.

Barrier dysfunction of the skin is considered central to AD[8]. *FLG*-null mutations are found in approximately 20–40% of patients with AD[43,94–96]. Filaggrin expression is downregulated in almost all cases of moderate to severe AD, irrespective of *FLG* mutations[97]. Netherton syndrome, in which mutations in *SPINK5*, which encodes a molecule that regulates stratum corneum formation, result in dysregulated desquamation, is characterized by AD-like dermatitis[98]. Defects in epithelial cell–cell contact can be related to AD-like dermatitis: defective tight junctions are associated with AD[99]. SAM syndrome (severe dermatitis, multiple allergies and metabolic wasting) is related to mutations in genes encoding components of epithelial cell–cell contact: *DSG1*, which encodes desmoglein-1[100], or *DSP*, which encodes desmoplakin[101]. The daily application of skin moisturizer that improves barrier function is recommended for the patients at all stages of severity and significantly reduces the incidence of AD development in infants[14].

T_H2 cytokines are known to impair barrier formation of the skin by inhibiting keratinocyte differentiation and diminishing tight junctions[40]. Consequently, it is reasonable to consider the positive loop of T_H2 inflammation and chronicity in AD. From the point of view of host defense, however, the barrier impairment effected by T_H2 cytokines seems to be a double-edged sword, because the fragility of the stratum corneum stimulates its removal, together with mites and/or poisons, by type 2 response–mediated scratching behavior, but it might allow these external agents to invade the body. The T_H2 loop is therefore assumed to be strictly regulated in the course of host-protective immune responses of the skin, whereas it is uncontrolled in AD.

The mechanistic link between barrier defects and the T_H2 response remains elusive[102]. An impaired barrier is expected to allow external agents such as allergens to enter the skin and accelerate the subsequent activation of immune cells. Consistent with that, LCs serve an essential role in the induction of T_H2 responses by epicutaneous sensitization with antigens in mice[63]. The impaired barrier also affects keratinocytes, sensory nerves and the skin microbiota, all of which can be involved in the initiation and propagation of T_H2 responses, as discussed above. Notably, the atopy-like phenotype of mice lacking the metalloproteinase ADAM17 (a disintegrin and metalloproteinase domain–containing protein 17) has been interpreted in three ways: it is due to the barrier deformity[103]; defective Notch signaling in keratinocytes results in dysregulated production of epidermal mediators such as TSLP[104]; or it allows the emergence of microorganisms and subsequent dysbiosis[105]. Thus, whereas the link between the barrier and the pathogenesis of AD is quite reasonable and understandable, the pathology of barrier impairment that distinguishes AD from healthy skin or other skin diseases remains obscure, because the damage to the skin barrier is not enough to drive the T_H2 loop in healthy people.

Impaired barrier function is also reported in psoriasis[106,107]. In vitro studies suggest that IL-17 downregulates filaggrin expression and impairs tight junctions of the skin[108,109]. Moreover, whereas the role of LCs in psoriasis pathogenesis is still controversial[59,79], barrier disruption is suggested to cause LCs to induce T_H17 responses[110]. Nevertheless, the impaired barrier does not seems to contribute to the IL-17 inflammatory loop[109] but instead drives the IL-4 loop in the skin (although only limited evidence suggests a contribution of barrier deformity to psoriatic inflammation[111]).

Therefore, one can speculate that both a physical defect and an additional defect in a unique component of the barrier might be specifically critical for the induction of type 2 responses and the subsequent development of AD.

Keratinocyte responses in AD

The epithelial tissues organize the microenvironment for the induction and propagation of type 2 or type 17 inflammation in the adjacent tissues beneath the epithelium[1]. Keratinocytes respond for the induction and propagation of inflammation in two phases (Fig. 1a): a primary response to the external stimuli, and a secondary response to the inflammatory loop of cytokines produced by immune cells. Type 2 and type 17 responses are originally effective at removing dangers from the epithelial surface: type 2 responses are directed against insects and poisons, while type 17 responses are directed against dermatophytes (Fig. 1c). The precise mechanism of the diverging point of the type of immune response is largely unknown, but studies suggest that the epidermis has phylogenetically acquired the ability to regulate each immune response to confront dangers at the front line of defense of the body.

In AD, the contribution of keratinocytes does not seem to depend largely on the nonspecific release of damage-associated molecular patterns but instead seems to depend on the active production of type 2 mediators following transcriptional initiation in response to upstream events (Fig. 4a). Keratinocytes produce cytokines such as TSLP, IL-25 and IL-33 following barrier disruption. Cytokines from keratinocytes can stimulate ILC2s, whose numbers are increased in the lesional skin of AD. ILC2s produce IL-5 and IL-13 and are involved in the unique type of immune response in AD[63]. Loss of Notch signaling via depletion of Notch1 and Notch2 simultaneously, or of the transcriptional regulator RBP-J, in keratinocytes induces the production of TSLP and the development of AD-like dermatitis[112]. TSLP enhances the maturation of DCs, and signaling via the TSLP receptor on LCs under epicutaneous sensitization with antigens has an essential role in the induction of the T_H2 response[63]. However, the production of TSLP by keratinocytes is also induced in psoriasis[113]. In addition, experimental evidence has suggested that the induction of TSLP expression from epithelial cells is not as indispensable as formerly thought for the induction and propagation of the T_H2 response[64,114]. Specifically, keratinocyte-specific depletion of TSLP impairs but does not abolish IL-4 production, IgE production or the development of atopy-like dermatitis in animal models with treatment with the vitamin D3 analog MC903[114] or with epicutaneous ovalbumin sensitization[64], whereas the depletion of a vitamin D receptor from keratinocytes completely

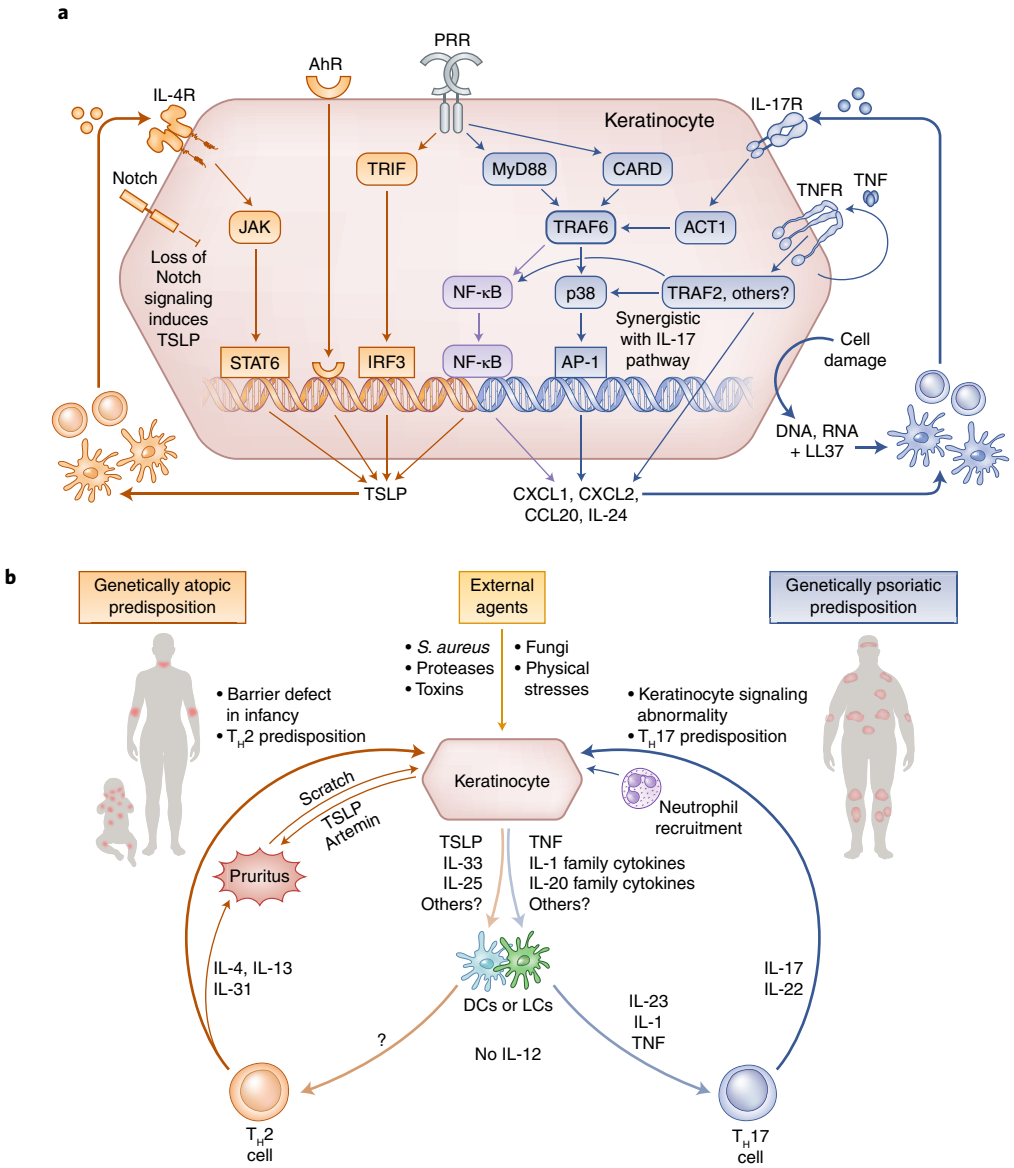


Fig. 4 | The type 2 EIME versus the type 17 EIME. a, Keratinocyte signaling pathways in AD (left; yellow) and psoriasis (right; blue). Keratinocytes are considered the primary sensors of external dangers at the surface of the body and interpreters and amplifiers for the elicitation and propagation of the appropriate type of immune response. In inflammatory skin diseases, the type of inflammation can be attributed to the disordered keratinocyte signaling machinery. In type 17 responses, TRAF6 mediates both primary stimuli by external danger signals and secondary stimuli by IL-17 and is therefore expected to be essential for the initiation and propagation of psoriatic inflammation by the EIME. The equivalent counterpart in type 2 responses remains to be identified, although both primary responses and secondary responses of keratinocytes contribute to the pathogenesis of AD. TNF is considered necessary for the IL-17 loop in psoriasis via the synergistic activation of IL-17 signaling in keratinocytes as well as the autoactivation of Tip-DCs. PRR, pattern-recognition receptor; MyD88, adaptor; ACT1, adaptor; TNFR, TNF receptor; AP-1, transcription factor; LL37, antimicrobial peptide. **b**, A 'mirror image' comparison of the IL-4 loop in AD (left; yellow) and the IL-17 loop in psoriasis (right; blue). Although the external stimuli are probably mostly similar, the barrier defects in infancy drive keratinocytes to induce the IL-4 inflammatory loop in AD, and keratinocyte signaling abnormalities in genetically predisposed people induce the IL-17 inflammatory loop by middle age in psoriasis. Further barrier dysfunction following pruritus contributes to the IL-4 loop. Although the IL-4 loop gives rise to the complication of other T_H2 cell–related diseases, such as asthma and food allergies, epidemiological evidence suggests that the IL-4 loop does not persist and thus AD can be sometimes spontaneously resolved by adolescence. Psoriasis is not complicated by other T_H17 cell–related diseases except metabolic syndrome and cardiovascular events, both of which are probably related to the critical involvement of TNF. Psoriasis develops during middle age and usually persists without treatment, which indicates that undetermined factors during aging persistently drive the IL-17 loop.

abolishes the induction of TSLP expression and subsequent generation of AD-like skin inflammation after topical treatment with MC903[62]. Consistent with that, studies of an animal model of Netherton syndrome with AD-like dermatitis suggest that signaling via the proteinase-activated receptor PAR2 in keratinocytes is involved in the expression of TSLP but is not essential for induction of the type 2 immune response[115]. Signaling via the transcription factor AhR (aryl hydrocarbon receptor) in keratinocytes contributes to the expression of TSLP and artemin, which seems to be related to the link between air pollution and the pathogenesis of AD[116].

Keratinocytes constitutively express IL-4R[117], and T_H2 cytokines directly activate keratinocytes in the second phase of keratinocyte responses in the inflammatory loop in AD (Figs. 3a and 4a). The direct stimulation of keratinocytes by T_H2 cytokines further induces the expression of epithelial type 2 mediators (such as TSLP) and barrier impairment, which completes the loop of IL-4 production and results in the propagation of type 2 inflammation.

Although it has been proposed for a long time that keratinocyte responses have a definitive role in the induction and propagation of AD inflammation, neither an epithelial factor nor the specific cellular machinery essential for the T_H2 response has been identified, except for signaling via the vitamin D receptor in an experimental animal model[62].

Keratinocyte responses in psoriasis

In psoriasis, keratinocytes are considered mainly targets of effector cytokines, such as IL-17 and IL-22, not a driver in the pathogenesis of this disease. Some familial cases of psoriasis, however, suggest that abnormal cellular signaling and transcriptional responses in keratinocytes might be responsible for psoriasis in genetically predisposed people, as discussed in the section above[56].

In animals, keratinocyte signaling pathways through TRAF6 (TNF receptor–associated factor 6), a key molecule in NF-κB and MAPK pathways, are required for the activation of skin-resident DCs and their IL-23 production, and the subsequent development of psoriatic dermatitis[76]. In addition, the full response of human keratinocytes requires the synergistic actions of IL-17 and TNF for the production of key inflammatory pathogenic mediators, such as IL-8, IL-17C and CCL20[26] (Fig. 4a). Such studies of the keratinocyte machinery in type 17 inflammation have stimulated research to identify the disordered homeostasis of epidermal NF-κB and MAPK signaling critical for organizing the psoriatic EIME (Fig. 4a).

Several lines of studies indicate that the target-cell type of IL-17-induced skin inflammation is keratinocytes[118,119]. T_H17 cytokines directly activate keratinocytes in the second phase of keratinocyte responses in the inflammatory loop in psoriasis (Figs. 3a and 4a). T_H17 cytokines further stimulate keratinocytes to produce psoriasis mediators (such as CCL20), which completes the loop of IL-17 production and results in the propagation of type 17 inflammation. Of note, TRAF6 is essential in both the primary phase and the secondary phase of keratinocyte responses in psoriatic inflammation: danger signaling and IL-17 signaling[76]. In addition, IL-17 signaling is also suggested to regulate keratinocyte proliferation and differentiation[120], which might underlie the pathology of psoriasis.

An epithelial product that is indispensable for psoriatic inflammation remains to be identified. However, cytokines of the IL-20 family[75,121–123] and IL-1 family[124] and lipid mediators[125] are all involved. It is notable that neutrophils are major and unique participants at the psoriatic EIME, and their infiltration into the epidermis is a critical sign of psoriasis histologically and immunologically[19,126]. Keratinocytes produce neutrophil chemoattractants, such as CXCL1 and CXCL2, in psoriatic inflammation and therefore the production of neutrophil chemoattractants is also considered an important contribution of keratinocytes.

Other results from animal studies suggest that keratinocytes are not actively involved but that their death and the subsequent release of their cellular contents and DC responses are important for psoriatic inflammation[127–129]. However, not keratinocyte death but parakeratosis — abnormal cornification with delayed exfoliation of keratinocytes in the stratum corneum — is a major histological sign of psoriasis. In this context, therefore, the prolonged residence of abnormally dying keratinocytes in the stratum corneum might trigger the DC responses in the pathogenesis of psoriasis.

Collectively, genetic studies have demonstrated that a genetic predisposition toward keratinocyte proinflammatory signaling is sufficient for the development of familial-type psoriasis[56], and animal studies have provided evidence that keratinocyte TRAF6 signaling has a pivotal role in the activation and propagation of the IL-23–IL-17 axis in psoriatic inflammation[76].

Box 1 | JAK inhibitors

JAK is a receptor-associated tyrosine kinase that is essential for the signaling cascade downstream of a series of cytokine-receptor pathways[158]. Several inhibitors targeting different JAKs have been developed, and some of them have been shown to be effective for AD by topical treatment[151,152],and for psoriasis by oral treatment[153–156] or topical treatment[154,157] (Table 2). The targets of JAK inhibitors are expected to be receptor signaling pathways for IL-4, IL-13 and IL-31 in AD, and for IL-23, IL-22 and the IL-20 family of cytokines in psoriasis (Table 3). Clinical evidence has not demonstrated strong links between the targeted JAKs and the pathogenesis of each disease. It is of note that PI3K and MAPK signaling pathways are also involved in most of these cytokine-receptor signaling pathways.

Sensory nerves in AD

The skin is innervated by a meshwork of peripheral nerves consisting of sparse autonomic fibers and abundant sensory fibers, along with inflammatory type 2 mediators, such as TSLP, IL-4 and IL-31[130–132], that drive the itching that exacerbates the disease via scratching. Here we question whether itching is involved in the primary pathogenesis of AD.

T_H2 cytokines such as IL-4 and IL-13 directly activate sensory neurons in both mice and humans[130]. Chronic itching is dependent on neuronal signaling via IL-4Rα and the kinase JAK1 (Box 1) in topical MC903–induced dermatitis. Patients with chronic itching recalcitrant to other immunosuppressive therapies markedly improve when treated with JAK inhibitors. TSLP secreted by epithelial cells in AD directly stimulates cutaneous sensory neurons to promote pruritus[131]. TSLP acts on a subset of $TRPA1^+$ sensory neurons to trigger robust itching-related behaviors. IL-31 is secreted mainly by activated T cells, especially T_H2 cells[132]. The IL-31 receptor is expressed in the peripheral nerves of mice and humans[133], which suggests that IL-31 secreted by T_H2 cells acts directly on peripheral nerves to cause the pruritus associated with AD[132,134]. After ligand binding, IL-31 signaling is mediated by activation of the JAK–STAT1–STAT5 (signal transducer and activator of transcription), ERK (MAPK) and PI3K (phosphoinositide-3-kinase) signaling pathways[135,136]. Nemolizumab, a monoclonal antibody to the IL-31 receptor, is effective in ameliorating the pruritus associated with AD, despite its limited effect on dermatitis[137]. Consistent with that, mice lacking JAK1 specifically in the nerves show less scratching behavior than do their wild-type counterparts in the animal model of MC903-induced AD, whereas the development of atopy-like dermatitis is unnaffected[130]. These results suggest that itching is not the primary cause of AD pathogenesis but is a key consequence of the T_H2 cytokine production in the skin (Fig. 3c).

Other internal and external pruritogens and their corresponding receptors are responsible for pruritus in AD. Histamine is a well-known pruritogen, although pruritus in AD is not controlled well by antihistamines[138,139]. Substance P, internal tryptases from mast cells and external proteases, such as those from dust mites and *S. aureus*, are also known to be involved in pruritus in AD[8,140].

It remains unknown if sensory nerves have roles in T_H2 cutaneous reactions, although studies have shed light on the relationship between sensory nerves and the T_H17 response (as described below). However, animal studies have demonstrated that in the intestine and lungs, deficiency in β2-adrenergic receptors results

Table 2 | Treatment of AD and psoriasis with JAK inhibitors

Drug	Target	Indication	Application
Tofacitinib	JAK3>JAK1>>(JAK2)	Moderate to severe AD	Topical[151]
JTE-052 (delgocitinib)	JAK1, JAK2, JAK3	Mild to moderate AD	Topical[152]
Tofacitinib	JAK3>JAK1>> (JAK2)	Plaque psoriasis	Oral[153,154], topical[154]
Baricitinib	JAK1, JAK2	Moderate to severe psoriasis	Oral[155]
Peficitinib	JAK1, JAK2, JAK3	Moderate to severe psoriasis	Oral[156]
Ruxolitinib	JAK1, JAK2	Plaque psoriasis	Topical[157]

Table 3 | JAK–STAT receptor signaling pathways of therapeutic target cytokines in AD and psoriasis

Cytokine	Indication of antibody therapies	Receptor	JAK	STAT	Targets in the skin
IL-4	AD	IL-4Rα, IL-2γc	JAK1, JAK3	STAT6	Lymphocytes, keratinocytes, sensory neurons
IL-13	AD	IL-4Rα, IL-13Rα1	JAK1, JAK2	STAT6	Lymphocytes, keratinocytes, sensory neurons
IL-31	AD	IL-31RA, OSMR	JAK1, JAK2	STAT1, STAT3, STAT5	Keratinocytes, sensory neurons
IL-23	Psoriasis	IL-23R, IL-12Rβ1	JAK2, Tyk2	STAT3, STA 4	Lymphocytes
IL-22	Psoriasis	IL-22R1, IL-10Rβ	JAK1, Tyk2	STAT1, STAT3, STAT5	Keratinocytes

OSMR, oncostatin M receptor.

in exaggerated ILC2 responses and type 2 inflammation, suggestive of a neuron-derived regulatory role for type 2 inflammation[141]. In addition, *S. aureus* directly interacts with nociceptor neurons and represses infection-induced pain and inflammation. Bacterial formyl peptides activate their nociceptors, and α-haemolysin induces pore assembly, which leads to calcium flux[142]. It is therefore intriguing whether *S. aureus* is involved in type 2 responses and AD pathogenesis via direct activation of sensory nerves. Thus far, it has been considered that type 2 responses directly induce the stimulation of sensory nerves[130–132] and that, conversely, the stimulation of sensory nerves directly induces type 17 responses (as discussed below)[83,143,144].

Sensory nerves in psoriasis

Clinical evidence suggests that peripheral nerves have a definitive role in the development and continuation of psoriatic lesions. Denervation reduces disease severity in patients with psoriasis or rheumatoid arthritis[145], and botulinum toxin type A is effective for the treatment of inverse psoriasis that appears only at flexural sites[146]. Consistent with that, patients with spinal-cord injuries have decreased levels of IL-23 and IL-17, as well as frequent fungal skin infections below the site of neurological lesions[147,148].

Published studies have shown that sensory nerves serve an essential role in type 17 immunity[83,143,144]. It has been reported that nociceptors interact with DCs and regulate the IL-23–IL-17 pathway via TRPV1 (transient receptor potential cation channel subfamily V member 1) in the psoriasis-like dermatitis model[144]. Consistent with that, *C. albicans* stimulates nociceptors via the C-type lectin receptor dectin-1 to induce the neuropeptide CGRP (calcitonin gene–related peptide)[149], and CGRP from TRPV1$^+$ nerves drives dermal DCs to produce IL-23 in the type 17 response to *C. albicans*[83]. It is therefore likely that the same mechanism exists in psoriasis, in which the same type of immune response is induced by TRPV1$^+$ nerves.

In contrast to its relevance to AD, pruritus is irrelevant to the definition of psoriasis regardless of whether an itchy sensation is associated with disease, and it is not considered to be part of the inflammatory loop in psoriasis.

Concluding remarks: new therapeutic strategies

Collectively, this Review has presented the positive feedback loop of the type 2 inflammation in AD and type 17 inflammation in psoriasis (Fig. 3a). The interplay of the epithelial tissue and the immune system completes each inflammatory loop. One must be aware that there is no loop without epithelial-cell factors: either barrier dysfunction or keratinocyte activation with the production of soluble mediators is an essential element in the development of both the loop of the microbiota and the immune system (Fig. 3b) and the loop of the sensory nerves and the immune system (Fig. 3c). Epithelial tissues are considered to be involved in the earliest events and in determining the type of immune responses that develop in the host-defense system at the outermost surface of the body[1]. Pathogenic immune responses in inflammatory skin diseases might simulate protective immune responses to pathogens (Fig. 1c). It is therefore reasonable to consider that epithelial tissues also serve a central role in determining the type of immune responses that develop in inflammatory skin diseases by organizing the type 2 EIME in AD and the type 17 EIME in psoriasis (Fig. 4b). This viewpoint raises questions and inspires further investigation into the dividing line between skin health and skin disease, which is the essence of determining which the type of skin immunity develops. In addition, it is of interest whether EIMEs in other organs, such as in the lungs and gut, have common or organ-specific roles in the protective immune responses and pathology of immune disorders.

EIMEs could be a new therapeutic target for the regulation of inflammatory loops. Biologics for the blockade of essential cytokines are powerful tools for the treatment of inflammatory skin diseases, especially psoriasis. So far, however, dermatologists have also been aware that continuous treatment with such biologics might be necessary for controlling psoriasis to permanently arrest the inflammatory loop. The features of the type 2 EIME in AD and the type 17 EIME in psoriasis described here are together expected to lead to the development of new therapies that modulate disease-specific EIMEs in the future.

Received: 13 July 2018; Accepted: 18 September 2018;
Published online: 16 November 2018

References

1. 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.* **76**, 81–89 (2014).
2. Bjerke, J. R. In situ characterization and counting of mononuclear cells in lesions of different clinical forms of psoriasis. *Acta Derm. Venereol.* **62**, 93–100 (1982).
3. Ellis, C. N. et al. Cyclosporine improves psoriasis in a double-blind study. *J. Am. Med. Assoc.* **256**, 3110–3116 (1986).
4. Gottlieb, S. L. et al. Response of psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis. *Nat. Med.* **1**, 442–447 (1995).
5. Hammar, H., Gu, S. Q., Johannesson, A., Sundkvist, K. G. & Biberfeld, P. Subpopulations of mononuclear cells in microscopic lesions of psoriatic patients. Selective accumulation of suppressor/cytotoxic T cells in epidermis during the evolution of the lesion. *J. Invest. Dermatol.* **83**, 416–420 (1984).
6. Mueller, W. & Herrmann, B. Cyclosporin A for psoriasis. *N. Engl. J. Med.* **301**, 555 (1979).
7. Faulds, D., Goa, K. L. & Benfield, P. Cyclosporin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in immunoregulatory disorders. *Drugs* **45**, 953–1040 (1993).
8. Kabashima, K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. *J. Dermatol. Sci.* **70**, 3–11 (2013).
9. Eichenfield, L. F. et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J. Am. Acad. Dermatol.* **70**, 338–351 (2014).
10. Furue, M. et al. Prevalence of dermatological disorders in Japan: a nationwide, cross-sectional, seasonal, multicenter, hospital-based study. *J. Dermatol.* **38**, 310–320 (2011).
11. Simpson, E. L. et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N. Engl. J. Med.* **375**, 2335–2348 (2016).
12. Kim, B. S. et al. Basophils promote innate lymphoid cell responses in inflamed skin. *J. Immunol.* **193**, 3717–3725 (2014).
13. Novak, N. & Bieber, T. Allergic and nonallergic forms of atopic diseases. *J. Allergy Clin. Immunol.* **112**, 252–262 (2003).
14. Horimukai, K. et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J. Allergy Clin. Immunol.* **134**, 824–830 (2014).
15. Oldhoff, J. M. et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* **60**, 693–696 (2005).
16. Paller, A. S., Kabashima, K. & Bieber, T. Therapeutic pipeline for atopic dermatitis: End of the drought? *J. Allergy Clin. Immunol.* **140**, 633–643 (2017).
17. Guttman-Yassky, E. et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: A randomized, double-blind, phase 2a trial. *J. Am. Acad. Dermatol.* **78**, 872–881 (2018).
18. Perera, G. K., Di Meglio, P. & Nestle, F. O. Psoriasis. *Annu. Rev. Pathol.* **7**, 385–422 (2012).
19. Lowes, M. A., Suárez-Fariñas, M. & Krueger, J. G. Immunology of psoriasis. *Annu. Rev. Immunol.* **32**, 227–255 (2014).
20. Kim, J. & Krueger, J. G. Highly effective new treatments for psoriasis target the IL-23/type 17 T cell autoimmune axis. *Annu. Rev. Med.* **68**, 255–269 (2017).
21. Lowes, M. A. et al. Increase in TNF-α and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). *Proc. Natl. Acad. Sci. USA* **102**, 19057–19062 (2005).
22. Serbina, N. V., Salazar-Mather, T. P., Biron, C. A., Kuziel, W. A. & Pamer, E. G. TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. *Immunity* **19**, 59–70 (2003).
23. Zaba, L. C. et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J. Exp. Med.* **204**, 3183–3194 (2007).
24. Zaba, L. C. et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J. Invest. Dermatol.* **129**, 79–88 (2009).
25. Zaba, L. C., Krueger, J. G. & Lowes, M. A. Resident and "inflammatory" dendritic cells in human skin. *J. Invest. Dermatol.* **129**, 302–308 (2009).
26. Chiricozzi, A. et al. Integrative responses to IL-17 and TNF-α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. *J. Invest. Dermatol.* **131**, 677–687 (2011).
27. Papp, K. A. et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *N. Engl. J. Med.* **376**, 1551–1560 (2017).
28. Kolls, J. K. & Lindén, A. Interleukin-17 family members and inflammation. *Immunity* **21**, 467–476 (2004).
29. Griffiths, C. E. et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* **386**, 541–551 (2015).
30. Krueger, J. G. et al. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J. Allergy Clin. Immunol.* **130**, 145–154 (2012).
31. Langley, R. G. et al. Secukinumab in plaque psoriasis–results of two phase 3 trials. *N. Engl. J. Med.* **371**, 326–338 (2014).
32. Lebwohl, M. et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N. Engl. J. Med.* **373**, 1318–1328 (2015).
33. Lin, A. M. et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J. Immunol.* **187**, 490–500 (2011).
34. Teunissen, M. B. M. et al. Composition of innate lymphoid cell subsets in the human skin: enrichment of NCR^+ ILC3 in lesional skin and blood of psoriasis patients. *J. Invest. Dermatol.* **134**, 2351–2360 (2014).
35. Villanova, F. et al. Characterization of innate lymphoid cells in human skin and blood demonstrates increase of $NKp44^+$ ILC3 in psoriasis. *J. Invest. Dermatol.* **134**, 984–991 (2014).
36. Fujita, H. The role of IL-22 and Th22 cells in human skin diseases. *J. Dermatol. Sci.* **72**, 3–8 (2013).
37. Tsai, Y. C. & Tsai, T. F. Anti-interleukin and interleukin therapies for psoriasis: current evidence and clinical usefulness. *Ther. Adv. Musculoskelet. Dis.* **9**, 277–294 (2017).
38. Shibata, S. et al. IL-27 activates Th1-mediated responses in imiquimod-induced psoriasis-like skin lesions. *J. Invest. Dermatol.* **133**, 479–488 (2013).
39. Chen, W. et al. Decreased expression of IL-27 in moderate-to-severe psoriasis and its anti-inflammation role in imiquimod-induced psoriasis-like mouse model. *J. Dermatol. Sci.* **85**, 115–123 (2017).
40. Egawa, G. & Kabashima, K. Multifactorial skin barrier deficiency and atopic dermatitis: Essential topics to prevent the atopic march. *J. Allergy Clin. Immunol.* **138**, 350–358 (2016).
41. Tsunemi, Y. et al. Interleukin-13 gene polymorphism G4257A is associated with atopic dermatitis in Japanese patients. *J. Dermatol. Sci.* **30**, 100–107 (2002).
42. Howard, T. D. et al. Identification and association of polymorphisms in the interleukin-13 gene with asthma and atopy in a Dutch population. *Am. J. Respir. Cell Mol. Biol.* **25**, 377–384 (2001).
43. Palmer, C. N. et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat. Genet.* **38**, 441–446 (2006).
44. Palmer, C. N. et al. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J. Allergy Clin. Immunol.* **120**, 64–68 (2007).
45. Esparza-Gordillo, J. et al. A common variant on chromosome 11q13 is associated with atopic dermatitis. *Nat. Genet.* **41**, 596–601 (2009).
46. Paternoster, L. et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. *Nat. Genet.* **44**, 187–192 (2011).
47. Ellinghaus, D. et al. High-density genotyping study identifies four new susceptibility loci for atopic dermatitis. *Nat. Genet.* **45**, 808–812 (2013).
48. Hirota, T. et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. *Nat. Genet.* **44**, 1222–1226 (2012).
49. Weidinger, S. et al. A genome-wide association study of atopic dermatitis identifies loci with overlapping effects on asthma and psoriasis. *Hum. Mol. Genet.* **22**, 4841–4856 (2013).
50. Tamari, M. & Hirota, T. Genome-wide association studies of atopic dermatitis. *J. Dermatol.* **41**, 213–220 (2014).
51. Anbunathan, H. & Bowcock, A. M. The molecular revolution in cutaneous biology: the era of genome-wide association studies and statistical, big data, and computational topics. *J. Invest. Dermatol.* **137**, e113–e118 (2017).
52. Armstrong, A. W., Harskamp, C. T. & Armstrong, E. J. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. *J. Am. Acad. Dermatol.* **68**, 654–662 (2013).
53. England, B. R., Thiele, G. M., Anderson, D. R. & Mikuls, T. R. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *Br. Med. J.* **361**, k1036 (2018).
54. Ha, C., Magowan, S., Accortt, N. A., Chen, J. & Stone, C. D. Risk of arterial thrombotic events in inflammatory bowel disease. *Am. J. Gastroenterol.* **104**, 1445–1451 (2009).
55. Atzeni, F. et al. Behçet's disease and cardiovascular involvement. *Lupus* **14**, 723–726 (2005).
56. Jordan, C. T. et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-κB, in psoriasis. *Am. J. Hum. Genet.* **90**, 796–808 (2012).
57. Marrakchi, S. et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N. Engl. J. Med.* **365**, 620–628 (2011).
58. Tsoi, L. C. et al. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. *Nat. Commun.* **6**, 7001 (2015).

59. Wohn, C. et al. Langerin^{neg} conventional dendritic cells produce IL-23 to drive psoriatic plaque formation in mice. *Proc. Natl. Acad. Sci. USA* **110**, 10723–10728 (2013).
60. Nakamura, Y. et al. Staphylococcus δ-toxin induces allergic skin disease by activating mast cells. *Nature* **503**, 397–401 (2013).
61. Van Dyken, S. J. et al. Chitin activates parallel immune modules that direct distinct inflammatory responses via innate lymphoid type 2 and γδ T cells. *Immunity* **40**, 414–424 (2014).
62. Li, M. et al. Topical vitamin D3 and low-calcemic analogs induce thymic stromal lymphopoietin in mouse keratinocytes and trigger an atopic dermatitis. *Proc. Natl. Acad. Sci. USA* **103**, 11736–11741 (2006).
63. Nakajima, S. et al. Langerhans cells are critical in epicutaneous sensitization with protein antigen via thymic stromal lymphopoietin receptor signaling. *J. Allergy Clin. Immunol.* **129**, 1048–1055 (2012).
64. Leyva-Castillo, J. M., Hener, P., Jiang, H. & Li, M. TSLP produced by keratinocytes promotes allergen sensitization through skin and thereby triggers atopic march in mice. *J. Invest. Dermatol.* **133**, 154–163 (2013).
65. Sokol, C. L., Barton, G. M., Farr, A. G. & Medzhitov, R. A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nat. Immunol.* **9**, 310–318 (2008).
66. Ohnmacht, C. et al. Basophils orchestrate chronic allergic dermatitis and protective immunity against helminths. *Immunity* **33**, 364–374 (2010).
67. Tang, H. et al. The T helper type 2 response to cysteine proteases requires dendritic cell-basophil cooperation via ROS-mediated signaling. *Nat. Immunol.* **11**, 608–617 (2010).
68. Halim, T. Y., Krauss, R. H., Sun, A. C. & Takei, F. Lung natural helper cells are a critical source of Th2 cell-type cytokines in protease allergen-induced airway inflammation. *Immunity* **36**, 451–463 (2012).
69. Motomura, Y. et al. Basophil-derived interleukin-4 controls the function of natural helper cells, a member of ILC2s, in lung inflammation. *Immunity* **40**, 758–771 (2014).
70. Hammad, H. et al. House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. *Nat. Med.* **15**, 410–416 (2009).
71. Lambrecht, B. N. & Hammad, H. The immunology of the allergy epidemic and the hygiene hypothesis. *Nat. Immunol.* **18**, 1076–1083 (2017).
72. Nowarski, R., Jackson, R. & Flavell, R. A. The stromal intervention: regulation of immunity and inflammation at the epithelial-mesenchymal barrier. *Cell* **168**, 362–375 (2017).
73. van der Fits, L. et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *J. Immunol.* **182**, 5836–5845 (2009).
74. Guttman-Yassky, E. et al. Major differences in inflammatory dendritic cells and their products distinguish atopic dermatitis from psoriasis. *J. Allergy Clin. Immunol.* **119**, 1210–1217 (2007).
75. Chan, J. R. et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J. Exp. Med.* **203**, 2577–2587 (2006).
76. Matsumoto, R. et al. Epithelial TRAF6 drives IL-17-mediated psoriatic inflammation. *JCI Insight* **3**, e121175 (2018).
77. Zhu, H. et al. RIG-I antiviral signaling drives interleukin-23 production and psoriasis-like skin disease. *EMBO Mol. Med.* **9**, 589–604 (2017).
78. Yoshida, K. et al. Distinct behavior of human Langerhans cells and inflammatory dendritic epidermal cells at tight junctions in patients with atopic dermatitis. *J. Allergy Clin. Immunol.* **134**, 856–864 (2014).
79. Yoshiki, R. et al. IL-23 from Langerhans cells is required for the development of imiquimod-induced psoriasis-like dermatitis by induction of IL-17A-producing γδ T cells. *J. Invest. Dermatol.* **134**, 1912–1921 (2014).
80. Belkaid, Y. & Tamoutounour, S. The influence of skin microorganisms on cutaneous immunity. *Nat. Rev. Immunol.* **16**, 353–366 (2016).
81. Williams, M. R., Nakatsuji, T. & Gallo, R. L. *Staphylococcus aureus*: master manipulator of the skin. *Cell Host Microbe* **22**, 579–581 (2017).
82. Lee, H. M. et al. Innate immune responses to *Mycobacterium ulcerans* via toll-like receptors and dectin-1 in human keratinocytes. *Cell. Microbiol.* **11**, 678–692 (2009).
83. Kashem, S. W. et al. Nociceptive sensory fibers drive interleukin-23 production from CD301b^{+} dermal dendritic cells and drive protective cutaneous immunity. *Immunity* **43**, 515–526 (2015).
84. Grice, E. A. & Segre, J. A. The skin microbiome. *Nat. Rev. Microbiol.* **9**, 244–253 (2011).
85. Kong, H. H. et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res.* **22**, 850–859 (2012).
86. Byrd, A.L. et al. *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. *Sci. Transl. Med.* **9**, eaal4651 (2017).
87. Langan, E. A. et al. The role of the microbiome in psoriasis: moving from disease description to treatment selection? *Br. J. Dermatol.* **178**, 1020–1027 (2018).
88. Ruiz-Romeu, E. et al. Microbe-dependent induction of IL-9 by CLA^{+} T cells in psoriasis and relationship with IL-17A. *J. Invest. Dermatol.* **138**, 580–587 (2018).
89. Loesche, M. A. et al. Longitudinal study of the psoriasis-associated skin microbiome during therapy with ustekinumab in a randomized phase 3b clinical trial. *J. Invest. Dermatol.* **138**, 1973–1981 (2018).
90. Alekseyenko, A. V. et al. Community differentiation of the cutaneous microbiota in psoriasis. *Microbiome* **1**, 31 (2013).
91. Gao, Z., Tseng, C. H., Strober, B. E., Pei, Z. & Blaser, M. J. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. *PLoS One* **3**, e2719 (2008).
92. Amaya, M. et al. Molecular analysis of Malassezia microflora in the lesional skin of psoriasis patients. *J. Dermatol.* **34**, 619–624 (2007).
93. Takemoto, A., Cho, O., Morohoshi, Y., Sugita, T. & Muto, M. Molecular characterization of the skin fungal microbiome in patients with psoriasis. *J. Dermatol.* **42**, 166–170 (2015).
94. van den Oord, R. A. & Sheikh, A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *Br. Med. J.* **339**, b2433 (2009).
95. Rodriguez, E. et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J. Allergy Clin. Immunol.* **123**, 1361–1370 (2009).
96. Weidinger, S. et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J. Allergy Clin. Immunol.* **118**, 214–219 (2006).
97. Howell, M. D. et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J. Allergy Clin. Immunol.* **120**, 150–155 (2007).
98. Chavanas, S. et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat. Genet.* **25**, 141–142 (2000).
99. De Benedetto, A. et al. Tight junction defects in patients with atopic dermatitis. *J. Allergy Clin. Immunol.* **127**, 773–786 (2011).
100. Samuelov, L. et al. Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat. Genet.* **45**, 1244–1248 (2013).
101. McAleer, M. A. et al. Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin. *J. Allergy Clin. Immunol.* **136**, 1268–1276 (2015).
102. Kubo, A., Nagao, K. & Amagai, M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. *J. Clin. Invest.* **122**, 440–447 (2012).
103. Franzke, C. W. et al. Epidermal ADAM17 maintains the skin barrier by regulating EGFR ligand-dependent terminal keratinocyte differentiation. *J. Exp. Med.* **209**, 1105–1119 (2012).
104. Murthy, A. et al. Notch activation by the metalloproteinase ADAM17 regulates myeloproliferation and atopic barrier immunity by suppressing epithelial cytokine synthesis. *Immunity* **36**, 105–119 (2012).
105. Kobayashi, T. et al. Dysbiosis and *Staphylococcus aureus* colonization drives inflammation in atopic dermatitis. *Immunity* **42**, 756–766 (2015).
106. Tagami, H. & Yoshikuni, K. Interrelationship between water-barrier and reservoir functions of pathologic stratum corneum. *Arch. Dermatol.* **121**, 642–645 (1985).
107. Takahashi, H., Tsuji, H., Minami-Hori, M., Miyauchi, Y. & Iizuka, H. Defective barrier function accompanied by structural changes of psoriatic stratum corneum. *J. Dermatol.* **41**, 144–148 (2014).
108. Yuki, T., Tobiishi, M., Kusaka-Kikushima, A., Ota, Y. & Tokura, Y. Impaired tight junctions in atopic dermatitis skin and in a skin-equivalent model treated with interleukin-17. *PLoS One* **11**, e0161759 (2016).
109. Gutowska-Owsiak, D. et al. IL-17 downregulates filaggrin and affects keratinocyte expression of genes associated with cellular adhesion. *Exp. Dermatol.* **21**, 104–110 (2012).
110. Doebel, T., Voisin, B. & Nagao, K. Langerhans cells - the macrophage in dendritic cell clothing. *Trends Immunol.* **38**, 817–828 (2017).
111. Nakajima, K. et al. Barrier abnormality due to ceramide deficiency leads to psoriasiform inflammation in a mouse model. *J. Invest. Dermatol.* **133**, 2555–2565 (2013).
112. Dumortier, A. et al. Atopic dermatitis-like disease and associated lethal myeloproliferative disorder arise from loss of Notch signaling in the murine skin. *PLoS One* **5**, e9258 (2010).
113. Volpe, E. et al. Thymic stromal lymphopoietin links keratinocytes and dendritic cell-derived IL-23 in patients with psoriasis. *J. Allergy Clin. Immunol.* **134**, 373–381 (2014).
114. Li, M. et al. Induction of thymic stromal lymphopoietin expression in keratinocytes is necessary for generating an atopic dermatitis upon application of the active vitamin D3 analogue MC903 on mouse skin. *J. Invest. Dermatol.* **129**, 498–502 (2009).
115. Briot, A. et al. Par2 inactivation inhibits early production of TSLP, but not cutaneous inflammation, in Netherton syndrome adult mouse model. *J. Invest. Dermatol.* **130**, 2736–2742 (2010).
116. Hidaka, T. et al. The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. *Nat. Immunol.* **18**, 64–73 (2017).

117. Junghans, V., Jung, T. & Neumann, C. Human keratinocytes constitutively express IL-4 receptor molecules and respond to IL-4 with an increase in B7/BB1 expression. *Exp. Dermatol.* **5**, 316–324 (1996).
118. Lambert, S., Swindell, W. R., Tsoi, L. C., Stoll, S. W. & Elder, J. T. Dual role of Act1 in keratinocyte differentiation and host defense: TRAF3IP2 silencing alters keratinocyte differentiation and inhibits IL-17 responses. *J. Invest. Dermatol.* **137**, 1501–1511 (2017).
119. Ha, H. L. et al. IL-17 drives psoriatic inflammation via distinct, target cell-specific mechanisms. *Proc. Natl. Acad. Sci. USA* **111**, E3422–E3431 (2014).
120. Wu, L. et al. A novel IL-17 signaling pathway controlling keratinocyte proliferation and tumorigenesis via the TRAF4-ERK5 axis. *J. Exp. Med.* **212**, 1571–1587 (2015).
121. Li, B. et al. Transcriptome analysis of psoriasis in a large case-control sample: RNA-seq provides insights into disease mechanisms. *J. Invest. Dermatol.* **134**, 1828–1838 (2014).
122. Kumari, S. et al. Tumor necrosis factor receptor signaling in keratinocytes triggers interleukin-24-dependent psoriasis-like skin inflammation in mice. *Immunity* **39**, 899–911 (2013).
123. Grinberg-Bleyer, Y. et al. Cutting edge: NF-κB p65 and c-Rel control epidermal development and immune homeostasis in the skin. *J. Immunol.* **194**, 2472–2476 (2015).
124. Rabeony, H. et al. IMQ-induced skin inflammation in mice is dependent on IL-1R1 and MyD88 signaling but independent of the NLRP3 inflammasome. *Eur. J. Immunol.* **45**, 2847–2857 (2015).
125. Yamamoto, K. et al. The role of group IIF-secreted phospholipase A2 in epidermal homeostasis and hyperplasia. *J. Exp. Med.* **212**, 1901–1919 (2015).
126. Taylor, P. R. et al. Activation of neutrophils by autocrine IL-17A-IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, RORγt and dectin-2. *Nat. Immunol.* **15**, 143–151 (2014).
127. Ganguly, D. et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. *J. Exp. Med.* **206**, 1983–1994 (2009).
128. Lande, R. et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* **449**, 564–569 (2007).
129. Zhang, L. J. et al. Antimicrobial oeptide LL37 and MAVS signaling drive interferon-β production by epidermal keratinocytes during skin injury. *Immunity* **45**, 119–130 (2016).
130. Oetjen, L. K. et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell* **171**, 217–228 (2017).
131. Wilson, S. R. et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell* **155**, 285–295 (2013).
132. Dillon, S. R. et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat. Immunol.* **5**, 752–760 (2004).
133. Cevikbas, F. et al. A sensory neuron–expressed IL-31 receptor mediates T helper cell–dependent itch: Involvement of TRPV1 and TRPA1. *J. Allergy Clin. Immunol.* **133**, 448–460 (2014).
134. Sonkoly, E. et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J. Allergy Clin. Immunol.* **117**, 411–417 (2006).
135. Cornelissen, C. et al. IL-31 regulates differentiation and filaggrin expression in human organotypic skin models. *J. Allergy Clin. Immunol.* **129**, 426–433 (2012).
136. Kasraie, S., Niebuhr, M. & Werfel, T. Interleukin (IL)-31 activates signal transducer and activator of transcription (STAT)-1, STAT-5 and extracellular signal-regulated kinase 1/2 and down-regulates IL-12p40 production in activated human macrophages. *Allergy* **68**, 739–747 (2013).
137. Ruzicka, T. et al. Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N. Engl. J. Med.* **376**, 826–835 (2017).
138. Cowden, J. M., Zhang, M., Dunford, P. J. & Thurmond, R. L. The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. *J. Invest. Dermatol.* **130**, 1023–1033 (2010).
139. Mollanazar, N. K., Smith, P. K. & Yosipovitch, G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clin. Rev. Allergy Immunol.* **51**, 263–292 (2016).
140. Kido-Nakahara, M., Furue, M., Ulzii, D. & Nakahara, T. Itch in atopic dermatitis. *Immunol. Allergy Clin. North Am.* **37**, 113–122 (2017).
141. Moriyama, S. et al. β_2-adrenergic receptor-mediated negative regulation of group 2 innate lymphoid cell responses. *Science* **359**, 1056–1061 (2018).
142. Chiu, I. M. et al. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* **501**, 52–57 (2013).
143. LaMotte, R. H., Dong, X. & Ringkamp, M. Sensory neurons and circuits mediating itch. *Nat. Rev. Neurosci.* **15**, 19–31 (2014).
144. Riol-Blanco, L. et al. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature* **510**, 157–161 (2014).
145. Joseph, T., Kurian, J., Warwick, D. J. & Friedmann, P. S. Unilateral remission of psoriasis following traumatic nerve palsy. *Br. J. Dermatol.* **152**, 185–186 (2005).
146. Zanchi, M. et al. Botulinum toxin type-A for the treatment of inverse psoriasis. *J. Eur. Acad. Dermatol. Venereol.* **22**, 431–436 (2008).
147. Nash, M. S. Known and plausible modulators of depressed immune functions following spinal cord injuries. *J. Spinal Cord Med.* **23**, 111–120 (2000).
148. Rubin-Asher, D., Zeilig, G., Klieger, M., Adunsky, A. & Weingarden, H. Dermatological findings following acute traumatic spinal cord injury. *Spinal Cord* **43**, 175–178 (2005).
149. Maruyama, K. et al. Nociceptors boost the resolution of fungal osteoinflammation via the TRP channel-CGRP-Jdp2 axis. *Cell Reports* **19**, 2730–2742 (2017).
150. Ray-Jones, H., Eyre, S., Barton, A. & Warren, R. B. One SNP at a time: moving beyond GWAS in psoriasis. *J. Invest. Dermatol.* **136**, 567–573 (2016).
151. Bissonnette, R. et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br. J. Dermatol.* **175**, 902–911 (2016).
152. Nakagawa, H., Nemoto, O., Igarashi, A. & Nagata, T. Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. *Br. J. Dermatol.* **178**, 424–432 (2018).
153. Bissonnette, R. et al. Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. *Br. J. Dermatol.* **172**, 1395–1406 (2015).
154. Bachelez, H. et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet* **386**, 552–561 (2015).
155. Papp, K. A. et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *Br. J. Dermatol.* **174**, 1266–1276 (2016).
156. Papp, K. et al. A phase 2a randomized, double-blind, placebo-controlled, sequential dose-escalation study to evaluate the efficacy and safety of ASP015K, a novel Janus kinase inhibitor, in patients with moderate-to-severe psoriasis. *Br. J. Dermatol.* **173**, 767–776 (2015).
157. Punwani, N. et al. Preliminary clinical activity of a topical JAK1/2 inhibitor in the treatment of psoriasis. *J. Am. Acad. Dermatol.* **67**, 658–664 (2012).
158. Schwartz, D. M. et al. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat. Rev. Drug Discov.* **16**, 843–862 (2017).

Competing interests

The authors declare no competing interests.

Additional information

Reprints and permissions information is available at www.nature.com/reprints.

Correspondence should be addressed to T.D. or K.K.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© Springer Nature America, Inc. 2018