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So close, and yet so far away: The dichotomy of the specific immune response and inflammation in psoriasis and atopic dermatitis

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Abstract. Schäbitz A, Eyerich K, Garzorz-Stark N (Karolinska Institutet; Karolinska University Hospital, Stockholm, Sweden; Technical University of Munich, Munich, Germany). So close, and yet so far away: The dichotomy of the specific immune response and inflammation in psoriasis and atopic dermatitis (Review). *J Intern Med* 2021; **290**: 27–39. https://doi.org/10.1111/joim.13235

Characterization of the complex interplay between cytokines, chemokines and microorganisms has led to a better understanding of the pathogenesis of both psoriasis and AD and resulted in new therapeutics targeting distinct immune responses. Psoriasis and AD share many characteristics: they are highly prevalent, chronic, cause primarily skin inflammation, but are associated with comorbidities, and come with a devastating quality of life due to itch and stigmatization. However, the pathogenesis of psoriasis and AD is opposing – psoriasis is dominated by a Th17 immune response that causes neutrophil migration, induction of innate immunity and exaggerated epithelial metabolism. Leading cytokines of this Th17 immune response are IL-17A and F, IL-22 and TNF-a. AD is characterized by Th2 immunity characterized by the signature cytokines IL-4 and IL-13 leading to an impaired epidermal barrier, dampened innate immunity and eosinophil migration. This review compares genetics, microbiome and T-cell infiltrate and resulting epithelial response in psoriasis and AD. Whilst the antagonistic course of psoriasis and AD is confirmed by response to specific biologics targeting the key cytokines of inflammation in psoriasis and AD, respectively, clinically overlapping phenotypes are challenging in our daily clinical practice. We conclude this review by summarizing what is known about these mixed phenotypes and how the identification of clinically relevant endotypes and molecular-driven decision-making is the next step in the field of dermato-immunology.

Keywords: atopic dermatitis, inflammatory skin disease, precision medicine, psoriasis, Th17, Th2.

Red, scaly and itchy: common denominators of psoriasis and AD

Psoriasis and AD share clinical and epidemiological hallmarks. Both diseases are common with prevalences ranging from 0.5% to 5% in adults all over the world; in children, the prevalence of AD may be up to 25% [1, 2]. Both diseases start early in life – AD typically in the first year of life, psoriasis either in puberty or in the mid-30s – and usually persist lifelong. Clinically, psoriasis and AD present with red and scaly skin, but they differ in predilection sites and morphology. Psoriasis is common at extensor sites of extremities, umbilicus and rectal tag, and may present in an inverse phenotype axillary and inguinal region [2] (Fig. 1a), whilst AD typically presents at the flexures and in adults as a head–neck–shoulder type (Fig. 1b) [3]; both diseases frequently occur at the capillitium, hand or feet, making differential diagnosis in these areas challenging. In terms of the clinical appearance, psoriasis lesions are sharply demarcated confluent papules, so-called plaques. They typically have a coarse lamellar scaling. The clinical picture is reflected/explained by the histopathological hallmarks of psoriasis (Fig. 1c-e). These include a thickened prickle cell layer (acanthosis), a thickened horny layer (hyperkeratosis) with nucleated keratinocytes due to accelerated/disturbed keratinization (parakeratosis), elongated epidermal rete ridges, dilated dermal tortuous capillaries and infiltration of neutrophils. In contrast, AD presents as a mixture of diffuse erythema,

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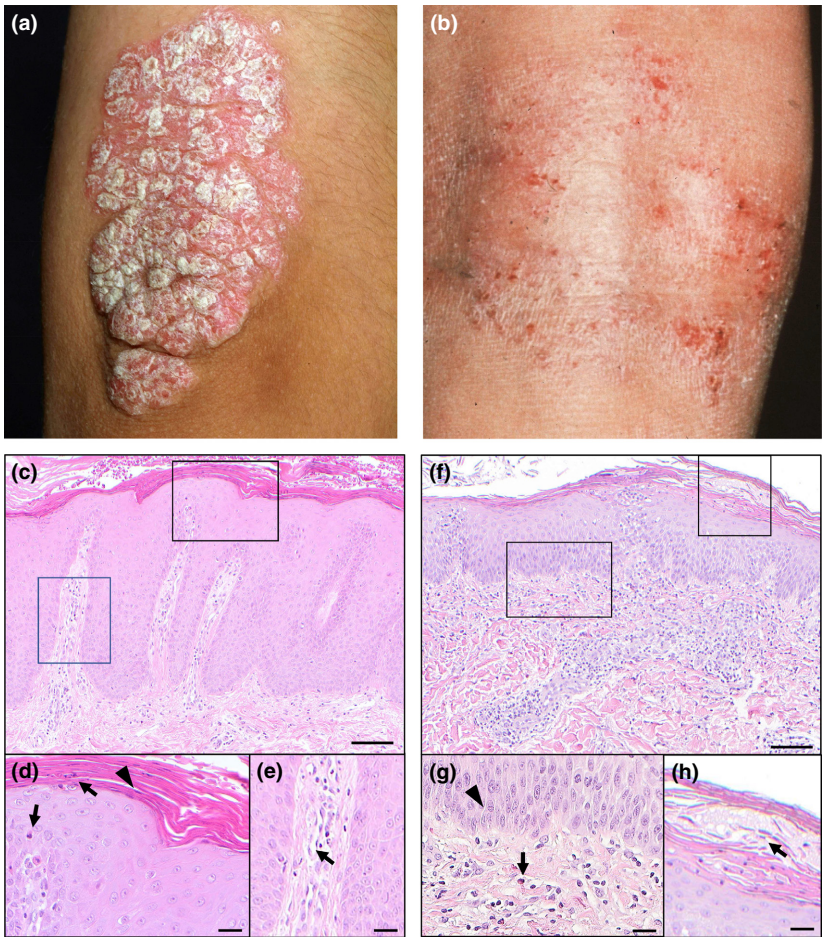

Fig. 1 *Typical clinical and histological features of psoriasis and AD. Psoriasis is characterized by well-demarcated plaques with gross lamellar silvery-white scales on extensor sites (a), whilst AD lesions are nondemarcated, typically present at flexural sites and present with fine lamellar scaling (b). Hallmarks of psoriasis on histopathological level (c, d and e) are regular acanthosis with elongated rete ridges, hyperparakeratosis (triangle in d), accumulation of neutrophils in the stratum corneum of the epidermis (arrows in d) and dilated vessels (arrow in e). In AD (f, g and h), hyperkeratosis, irregular acanthosis, spongiosis (triangle in g), eosinophilic infiltrate (arrow in g) and serum crusts (arrow in h) dominate the histological picture. Scale bars in C and F: 100 μm, scale bars in d, e, g and h: 25 μm.*

papules, vesicles, erosions, crusts and fine lamellar scaling – this mixture of efflorescences is the definition of the term 'eczema'. On histopathological level, this is reflected by intercellular oedema between keratinocytes (spongiosis), acanthosis and hyperkeratosis in chronic eczema with the absence of nuclei (orthokeratosis) and increased numbers of eosinophils and mast cells (Fig. 1f-h). A cardinal symptom of AD is itch. Whilst older dermatology textbooks state psoriasis is not itchy, this is now revised as many psoriasis patients also report an itchy skin. In fact, itch determined by specific scores such as the ItchyQoL is comparable between psoriasis and AD patients [4].

Both psoriasis and AD are chronic inflammatory diseases that primarily affect the skin, but at least in severe forms have a systemic component. Psoriasis can manifest as psoriatic arthritis or ocular psoriasis and is associated with several comorbidities, including metabolic syndrome, inflammatory bowel diseases, anxiety and depression, and cardiovascular abnormalities [5] (Table 1). AD, allergic asthma and allergic rhinoconjunctivitis build the atopic diseases that can all manifest in one patient.

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Table 1. *Comorbidities of psoriasis and AD*

	Psoriasis	AD
Infections	Inconsistent data	-Skin infections such as herpes simplex, molluscum contagiosum, impetigo -Respiratory tract infections, gastroenteritis, urinary tract infection
Allergic comorbidities	Limited data on possible association with -Asthma (no data if asthma is allergy-related) -Allergic rhinitis	-Allergic asthma) -Food allergy -Allergic rhinitis -Allergic contact dermatitis -Hand dermatitis -Irritant contact dermatitis
Neuropsychiatric disorders	-Anxiety -Depression -Suicidal ideation	-ADHD -Anxiety -Depression -Suicidal ideation -Epilepsy (children)
Cardiometabolic disorders	-Metabolic syndrome and its individual conditions (obesity, hyperlipidaemia, diabetes, arterial hypertension) -Atherosclerosis -Atrial fibrillation -Major adverse cardiovascular events (MACE), in particular myocardial infarction	-Obesity -Coronary artery disease, congestive heart failure
Autoimmune diseases	-Crohn's disease -Ulcerative colitis -Caeliac disease -Rheumatoid arthritis -Multiple sclerosis	-Crohn's disease -Ulcerative colitis -Caeliac disease -Alopecia areata
Malignancies	-Inconsistent data	-Lymphoma

Overview of comorbidities in atopic dermatitis. Modified from [10-12] and Andersson A.M. et al. Update on comorbidities in psoriasis. Current Dermatology Reports, 2017.

AD is also associated with inflammatory bowel disease, cardiovascular and neuropsychiatric comorbidities [6] (Table 1) The development of malignancies is under controversial debate in both psoriasis and AD as this may depend on the type of malignancy and on the individual patient, in particular long-term therapies [7].

The combination of itchy, inflamed and scaly skin with stigmatization and comorbidities results in a devastating quality of life of many patients with either psoriasis or AD. In fact, the quality of life in affected children is reduced to a degree comparable with diabetes, cystic fibrosis or cancer [8]. Skin disorders rank at the fourth position in the global burden of disease analysis regarding years lived with disability [9]. In summary, psoriasis and AD are similar in terms of their high frequency, loss of quality of life and primary presentation as skin diseases with potential systemic inflammation and comorbidities. They differ, however, in their precise clinical phenotype and the comorbidity spectrum.

The immunopathogenesis of psoriasis and AD

Genetic aspects

Both psoriasis and AD are based at least partially on a genetic background. In monogenetic twins, the concordance rate of either psoriasis or AD is higher than in dizygotic twins. The complex trait of both

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Table 2. *Genetics of psoriasis and AD*

	Psoriasis			Atopic dermatitis		
	Gene	Protein	Pathway/function	Gene	Protein	Pathway/function
Epidermal barrier	LCE3B and LCE3C (1q21, PSORS4 locus)	Late cornified envelope 3B and 3C	Keratinocyte differentiation	FLG	Filaggrin (1q21)	Keratinocyte differentiation
	GJB2 (13q11) (connexin-26)	Gap Junction protein beta-2 (connexin 26)	Keratinocyte stability	SPINK5 (5q32)	Protease inhibitor LEKTI	Keratinocyte differentiation
Innate immune response	TNFAIP3 (6q23.3)	Tumour necrosis factor, alpha-induced protein 3 (inhibitor of TNF-induced NF-κB activation)	NF-κB pathway	TLR2 (4q31) and TLR9 (3p21)	Toll-like receptors 2 and 9	Toll-like receptor signalling
	CARD14 (17q25, PSORS2 locus)	Caspase recruitment domain-containing protein CARMA2	NF-κB pathway	CARD4 (7p15-p14)	Caspase recruitment domain-containing protein	NOD-like receptor signalling pathway
	FBXL19 (16p11)	Inhibitor of NF-κB activation	NF-κB pathway	DEFB1 (18p23)	Human β-defensin	Antimicrobial immune response
	REL (2p16)	NF-κB-subunit	NF-κB pathway			
	IFIH1/MDAS (2q24)	Antiviral receptor	IFN signalling			
	TYK2 (19p13)	Tyrosine kinase 2	IFN signalling			
Acquired immune response	HLA-C (6p21, PSORS1 locus)	MHC class I	Antigen presentation	FCER1A (1q23) and FCER1G (1q23)	High-affinity immunoglobulin epsilon receptor subunit alpha and subunit gamma	IgE immune response
	IL-23R (1p31)	IL-23 receptor	IL-23 signalling	FCER1B (11q12)	High-affinity immunoglobulin epsilon receptor subunit beta	IgE immune response
	IL-12B (5q33)	IL-12/IL-23p40-subunit	IL-23 signalling	IL-4 and IL-13 (5q31–33)	Interleukin-4 and Interleukin-13	IL-4, IL-13 signalling
	IL-23A (12q13)	IL-23 p19 subunit	IL-23 signalling	IL-4R (16p12)	Interleukin-4 receptor	IL-4, IL-13 signalling

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Table 2 (*Continued*)

Psoriasis			Atopic dermatitis		
Gene	Protein	Pathway/function	Gene	Protein	Pathway/function
STAT3 (17q21)	Signal transducer and activator of transcription 3	Th17 differentiation	STAT6 (12q13)]	STAT6 protein	IL-4 signalling
TRAF3IP2 (6q21)	Adapter protein CIKS (IL-17 receptor adaptor)	IL-17 and NF-κB signalling	IL-31 (12q24)	Interleukin-31	IL-31 signalling

Selection of susceptibility genes associated with AD or psoriasis, modified according to [3, 24].

diseases is mirrored by the number of genetic loci associated with either psoriasis or AD, respectively.

More than 80 susceptibility loci for psoriasis have been identified to date, most of them in gene regions controlling epidermal architecture or function, as well as the innate immunity or the Th17 pathway [13, 14] (Table 2). The by far highest association is shown for the HLA-Cw6 allele. Major antigens identified in psoriasis are processed and presented via HLA-Cw6 [15]. HLA-Cw6 has also been shown to be associated with an improved outcome of therapies with methotrexate or ustekinumab [16, 17].

The strongest genetic risk factor for AD is a loss-of-function mutation in the gene *filaggrin* [18]. *Filaggrin* is critically involved in the epidermal barrier, and its loss leads to increased permeability of the skin [19]. Besides filaggrin, more than 30 genetic loci have been identified to be associated with AD [20, 21]. Besides *filaggrin*, variants in the *IL-13* gene or the *IL-6 receptor* region and multiple rare protein-coding variants explain close to 30 per cent of the total AD heritability [22].

Given the central role for the epidermal structure and the immune system for both psoriasis and AD, it is not surprising that both diseases share risk loci. Interestingly, comparative studies revealed that shared loci are inversely correlated with positive or negative associations to psoriasis or AD, respectively [23]. Thus, both psoriasis and AD show a complex trait heritability with multiple identified genetic loci, but genetically speaking, psoriasis and AD are antagonistic.

Microbiome

Increasing evidence suggests the microbiome is centrally involved in the pathogenesis of inflammatory skin diseases. In AD, colonization of the skin with the commensal bacterium *S. aureus* is described since decades. *S. aureus* is detectable on nonlesional skin in most AD patients, and there is evidence that *S. aureus* abundance correlates with disease flares [25] and severity [26]. *S. aureus* impacts epidermal barrier function [27] and host immune response via secretion of proteases [28] or superantigens [29, 30]. Whilst it is still unclear whether *S. aureus* colonization is an epiphenomenon or the primary causative factor of skin inflammation in an AD endotype, technical advances investigating the whole skin microbiome

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in AD have confirmed that AD is dominated by one microbe – *S. aureus* [31]. Attempts to therapeutically make use of this include early barrier protection using emollients in newborns and infants at risk [32], as well as topical or oral probiotics aiming at normalizing the skin microbiome in AD. Whilst initial reports were encouraging, no breakthrough has been achieved at a global AD level with both attempts [33-35] – a fact that points to the need of personalized approaches and better definition of disease endotypes.

A large study comparing the microbiome associated with the corresponding lesional skin transcriptome in AD versus psoriasis revealed that psoriasis is not dominated by one or few microbes. *Corynebacterium* spp. seem to be frequently present on the skin, but their role is currently unknown [36]. Besides the cutaneous microbiome, there are numerous studies reporting that the gut microbiome is altered in psoriasis patients [37]; however, these studies are highly heterogeneous and do not allow final conclusion yet. In summary, the microbiome differs in psoriasis and AD, with AD being dominated by *S. aureus* and psoriasis being diverse in terms of skin-colonizing species.

T-cell infiltrate and immune response pattern

The vast majority of inflammatory skin diseases is characterized by an interaction of the lymphocytic infiltrate in the skin and keratinocytes [38]. Whilst psoriasis is dominated by a Th17 type immune response, AD is a type Th2-mediated disease [39] (Fig. 2, Table 3). For psoriasis, the immune cascade is well-described and also verified by specific therapeutics with enormous efficacy. Briefly, antigen-presenting cells such as plasmacytoid dendritic cells and myeloid dendritic cells promote the differentiation of naïve CD4 + T cells into Th17 cells under a micro-environment containing IFN-α, IL-1β, and IL-6 and IL-12. The Th17 phenotype is stabilized by IL-23. Th1 and Th17 cells, but also Th22 cells, migrate to the skin and release cytokines, predominantly TNF-a, IL-17A, IL-17F, IL-21, IL-22 and IL-29 [40-42]. Collectively, these cytokines account for nearly all hallmarks of psoriasis: IL-17A/F and IL-22 in synergism with each other and with TNF-α induce secretion of antimicrobial peptides in human keratinocytes [43, 44]. IL-17A/F also induce secretion of the chemokine CXCL8 in keratinocytes, which leads to migration of neutrophil granulocytes in the skin [45]. In parallel, IL-21 and IL-22 inhibit keratinocyte differentiation and response to apoptotic stimuli and thus induce excessive proliferation of the epidermis, so-called acanthosis and parakeratosis [46]. This opens up a *vicious circle*, as antimicrobial peptides trigger T-cell responses [47] and other keratinocyte factors such as IL-17C [48] or IL-1 cytokines that contribute to the early pathogenesis of psoriasis.

The immune infiltrate of AD, in contrast, is more heterogeneous and also depends on the inflammatory kinetics. Very early and acute AD is characterized by Th2 cells almost exclusively [29, 49],

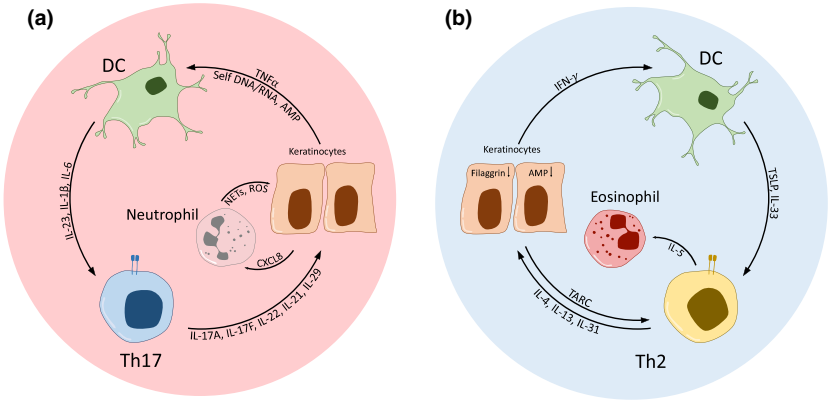

Fig. 2 *The pathogenesis of psoriasis (blue circle) and atopic dermatitis (red circle). Central cellular mediators open up vicious circles with pro-inflammatory mediators in both diseases – dominated by Th2 immunity, impaired epidermal barrier and epithelial immunity, as well as eosinophils in AD and Th17 immunity with induced metabolism, de-differentiation of keratinocytes and induced epithelial immunity in psoriasis.*

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Table 3. *Immune response in psoriasis and AD (modified from [68])*

	Psoriasis	Atopic dermatitis
Immune response pattern	Th17 type immune response, reflected by parakeratosis, dilated capillaries, micro-abscesses	Th2 type immune response, reflected by impaired epidermal barrier/ spongiosis
T-cell infiltrate	Th17 cells, Th1 cells, Th2 cells	Th2 (acute) Th2, Th22 and Th1 (chronic)
Other immune cells	pDCs, neutrophils	eosinophils
Cytokines	TNF-a, IL-17A, IL-17F, IL-21, IL-22, IL-29 CXCL-8	IL-4, IL-5, IL-13, IL-31, IL-33, TSLP
Putative (auto)antigens	Humoral autoantigen: gliadin T-cell autoantigens: LL37, ADAMTSL5, desmogleins, keratins, lipids	Environmental antigens (birch and grass pollen, house dust mite), humoral autoantigens: manganese superoxide dismutase, Hom s 1-5, S100A12, others; T-cell autoantigens: Hom s 2, thioredoxin

whilst in addition to Th2 cells other T-cell subsets such as Th1, Th17 and Th22 cells are observed in more chronic disease [50, 51]. The Th2-dominated T-cell response in AD leads to (1) isotype switch and humoral immunity, (2) recruitment of eosinophil granulocytes and (3) direct impact on the epidermis. Whilst the relevance of the IL-4-mediated isotype switch towards IgE for the pathogenesis of AD is still under debate [52, 53], both eosinophil recruitment by IL-5 and impact on the epidermis are hallmarks of inflamed AD skin. In particular, the direct impact of IL-4 and IL-13 on the epidermis reflects the AD phenotype. Both cytokines downregulate genes of the epidermal differentiation complex such as filaggrin [54] and also impair the induction of immune-related factors such as antimicrobial peptides in keratinocytes [29]. Th2 immunity is also associated with itch both via direct activation of itch-sensory neurons [55, 56] and via secretion of mediators such as IL-31 [57]. Also in AD, keratinocyte-derived products such as IL-33 [58] or TSLP influence the ongoing immune response and thus open up a *vicious circle* [59]. Proliferation of keratinocytes resulting in epidermal hyperplasia, a hallmark of chronic disease, is mainly driven by IL-22, which is secreted by Th22 cells [46, 60].

The immune response in psoriasis or AD is determined by the genetic background as described above, but also by the nature of T-cell antigens. In psoriasis, described antigens are the antimicrobial peptide LL37 [47] or the melanocyte antigen ADAMTSL5 [61]. In murine models of psoriasis, also desmosomal components such as desmogleins [62] or keratins as important regulators of keratinocyte differentiation are described to induce a psoriasis-like phenotype. Thus, even though it is not finally proven that these antigens are causative, plaque-type psoriasis may be regarded as an autoimmune disease.

In AD, several environmental antigens such as birch or grass pollen or house dust mite are described to be associated with the cutaneous inflammation. However, just like in psoriasis it is unclear whether these antigens are an epiphenomenon or causative for AD development. A subset of AD patients does react with acute eczematous reactions to epicutaneous challenge with these aero-allergens. This can be tested with the so-called atopy patch test [63, 64]. However, controlled clinical trials investigating immune desensitization protocols in AD patients did not result in an improved outcome of skin inflammation [65, 66]. This is controversially discussed as one cannot exclude the possibility that subtypes of AD patients may benefit from desensitization protocols. In any case, it is accepted that many of the antigens associated with AD induce a type 2 immunity micro-environment. For example, pollen contains lipid mediators that drive Th2 development and inhibit other immune responses such as Th1 [67]. Taken together, Th17 cells are central for the pathogenesis of psoriasis, whilst AD is mediated by Th2 cells.

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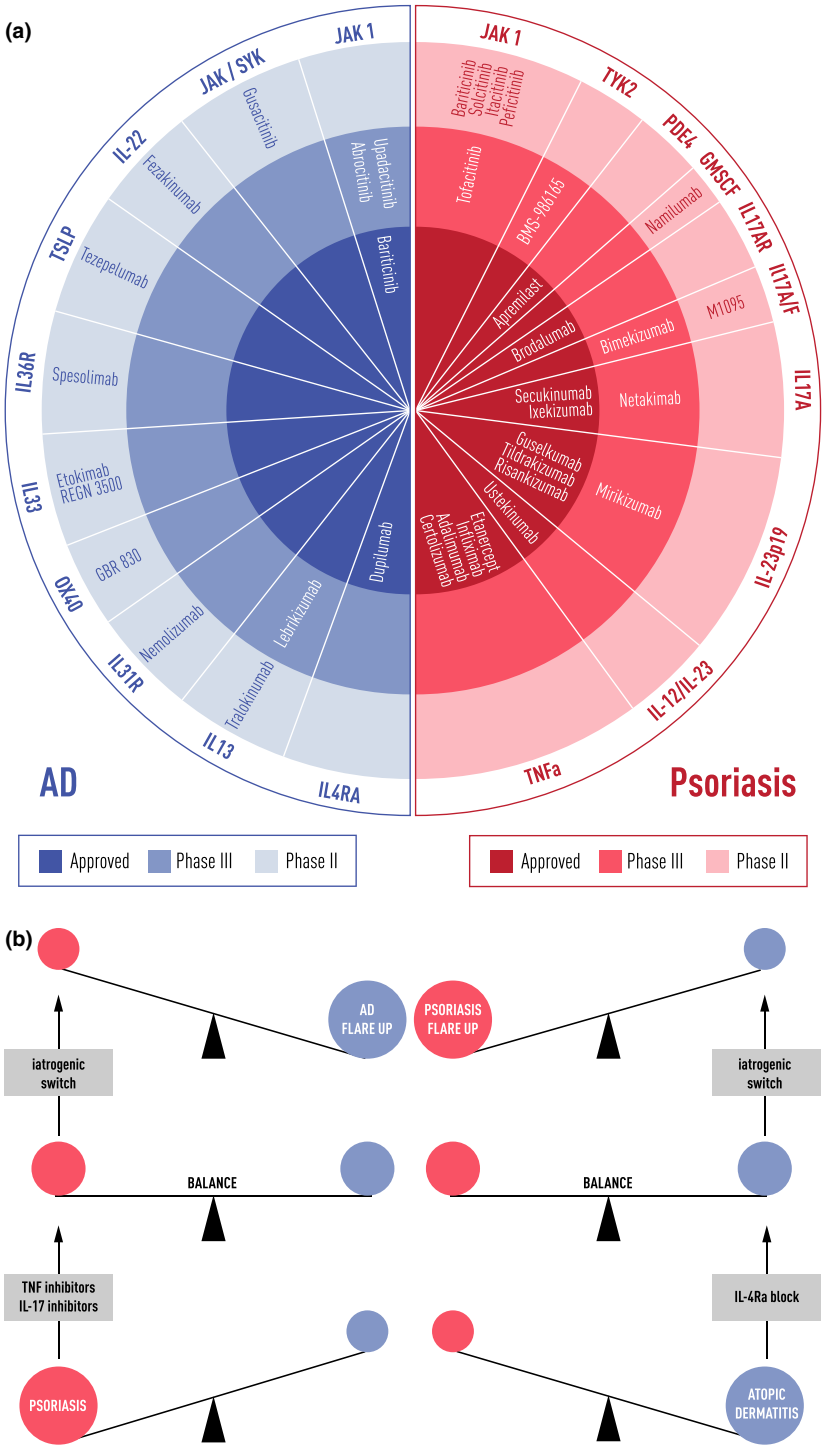

Fig. 3 *Therapeutic landscape and insights from specific therapies. Approved therapies for psoriasis and AD and selection of therapeutic agents in phase II and phase III (a). Novel therapies specifically interfering with Th17 or Th2 immunity may iatrogenically shift the balance of both immune response patterns. In certain cases, this may result in induction of the antagonistic disease (AD in psoriasis patients as shown in b).*

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In summary, the immunopathogenesis of psoriasis and AD is diverse – psoriasis is characterized by a Th17-induced activation of innate immunity including neutrophil migration into the skin and exaggerated metabolism and excessive keratinocyte proliferation. AD is characterized by Th2 type immunity that leads to isotype switch towards IgE, recruitment of eosinophils and a decreased epidermal barrier and innate immunity.

Insights from specific therapies

Whilst the therapeutic options to treat inflammatory skin diseases were very unspecific for around two centuries, dermatology is awaking from its Sleeping Beauty now that we have a palette of highly specific biologic therapies and even more therapies to come (Fig. 3a). TNF inhibitors and even more so IL-17 or IL-23 inhibitors are highly effective to treat psoriasis, with average skin improvement rates of up to 90% after a few months of treatment. Since 2017, there is also one biologic available to treat AD, namely the IL-4Ra-blocking antibody dupilumab [69]. Many more Th2-directed therapies such as IL-13 inhibitors are close to approval in the United States and Europe [70]. Thus, the insights into immunology and immune response patterns led to targeted endstream therapies in both psoriasis and AD.

The other side of the coin is that these specific therapies require a precise and correct diagnosis. In contrast to conventional systemic therapies such as methotrexate or cyclosporine that have beneficial effects in both psoriasis and eczema, biologics approved for psoriasis are not effective in AD patients at least at population level – and *vice versa*, dupilumab is not expected to be efficient in psoriasis.

In fact, biologics interfering with one distinct lymphocyte subset allow insights into the pathogenesis of inflammatory skin diseases. This observation has first been made in a rare group of patients that suffer from both psoriasis and AD. As the underlying immune responses are mutually antagonistic, these patients have a flip-flop-like development of either psoriasis or AD over time [39, 71]. If such a patient receives TNF inhibitors, psoriasis may improve, but at the same time AD flares up [39] (Fig. 3b). Also in the general population, TNF inhibitors may induce eosinophilia and dry skin as well as eczema or dermatitis [72]. This phenomenon is not limited to TNF inhibitors, but also observed in newer and even more efficient psoriasis biologics that inhibit IL-17 [73, 74].

This iatrogenic switch from psoriasis to AD or eczema is also observed the other way round: also the AD-specific biologic dupilumab may induce psoriasis-like skin lesions. This has been published in several patients that were treated for AD with dupilumab and subsequently developed psoriasis plaques [75-77]. In summary, classical psoriasis and AD are antagonistic, and with specific therapies designed for psoriasis or AD, the respective other disease may be induced iatrogenically (Fig. 3).

Mixed phenotypes pose diagnostic and therapeutic challenges

Although classical psoriasis and AD are unequivocally distinguishable at large (Table 4), a variety of phenotypes showing features of both psoriasis and AD pose enormous diagnostic and therapeutic challenges. In a comparative study of childhood psoriasis and atopic dermatitis, only 10 % of children with psoriasis were correctly diagnosed by the referring physicians, whilst 79.9 % of patients with psoriasis were misdiagnosed as AD [78]. But even specialists struggle with diagnostic uncertainty. In a prospective study analysing 100 consecutive psoriasis patients of a department of dermatology, the authors found that 20% presented with an intermediate phenotype showing lesions with characteristics of both eczema and psoriasis [79]. Eventually, these overlapping cases are often diagnosed as 'psoriasiform eczema', 'eczematous psoriasis' or 'sebopsoriasis'. This diagnostic dilemma is exemplified by the differential diagnosis palmoplantar psoriasis and chronic hand and foot dermatitis: both psoriasis and eczema on palmoplantar sites may present with patterns ranging from predominantly pustular or papulovesicular lesions to thick, hyperkeratotic lesions [80, 81]. On histological level, characteristic features such as thickening of the epidermis (acanthosis) and increased abnormal epidermal proliferation (hyperparakeratosis) are shared by both diseases [80, 82, 83]. In a recently published study by the Dermatology Department of the University of Magdeburg/Germany, the authors demonstrate that in a cohort of 132 patients suffering from unclear palmar chronic inflammation, only 55 patients received a clear diagnosis of either hand eczema or palmar psoriasis, whereas due to a mixed histological picture a clear diagnosis could not be given for 77 patients [84]. Thus,

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Table 4. *Hallmarks of psoriasis and AD diagnostics*

	Typical atopic dermatitis	Typical psoriasis
Clinical picture	Onset in childhood	Onset adolescence or early adulthood
	Flexural sites	Extensor sites
	Fine lamellar scaling	Gross lamellar scaling
	Nondemarcated	Demarcated plaques
	Serum crusts	Dry lesions
	(Intense) itch	(Mild) itch
Histolological picture	Regular hyperkeratosis	Hyperparakeratosis
	Orthogranulosis	Hypogranulosis
	Irregular acanthosis	Regular acanthosis with elongated rete ridges
	Eosinophils, mast cells	Neutrophils
	Spongiosis	No spongiosis
	Vasodilatation without neoangiogenesis	Dilated tortuous capillaries, neoangiogenesis
Typical manifestation and comorbidities	Allergic asthma	Psoriatic arthritis
	Allergic rhinitis	

current diagnostics needs to be complemented by advanced diagnostic tools to differentiate psoriasis from AD and, moreover, to address so far unresolved questions such as response to therapy or development of comorbidities. This seems challenging, as also on cellular and molecular level the picture of psoriasis and eczema is not as crystal clear as it seems at first glance. Cohen and colleagues recently showed that percentages of Th2 and Th17 cells cannot be used to reliably discriminate biopsy specimens of psoriasis and eczema [85]. On molecular level, we and others found that psoriasis and eczema indeed share a substantial number of commonly regulated genes and pathways related to antimicrobial response, epidermal differentiation and immune response [86-89]. However, unique molecular markers for differential diagnostics have been suggested. Expression of IL-36 [85, 90] or CCL26 in lesional skin has been proposed to discriminate psoriasis from eczema [91]. Yet, both markers have not been validated in larger cohorts with clinically and histologically unclear cases. To identify true AD and psoriasis-specific disease signatures, we investigated the rare population of patients affected by both psoriasis and eczema at the same time [39]. This enabled us to intra-individually compare antagonistic inflammatory responses in the same organ [39]. Indeed, by performing intra-individual genome expression analysis of biopsy specimens from patients of this rare cohort we identified unique disease signatures [88]. Resulting from this analysis, two markers, NOS2 and CCL27, were identified that not only correlated with hallmarks of either psoriasis or eczema but also diagnosed psoriasis and eczema with a sensitivity and specificity of >95%. Moreover, the NOS2- and CCL27-based classifier predicted the correct diagnosis, which was in line with therapeutic response to drugs acting specifically on psoriasis or eczema, respectively [39, 92-96].

In summary, phenotypes and immune response patterns may overlap between both AD and psoriasis reflecting the high heterogeneity of both diseases. Therefore, more precise diagnostic tools and reliable predictive models for response to therapy or development of comorbidities are urgently needed.

Conclusion and outlook

The traditional disease classification in dermatology is based on clinical phenotyping and histological architecture of lesional skin. Whilst this classification is impressively accurate in most cases, therapeutics that are available today and specifically target key mediators of disease pathogenesis show its limitations, namely a substantial number of nonresponders to all therapies. With a better understanding of immunology and availability of research techniques, the pathogenesis of both psoriasis and AD is nowadays understood in large parts – the genetic basis, environmental factors,

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T-cell responses and their effect at epithelial cells. Whilst central questions such as early triggers and factors leading to chronic inflammation remain poorly understood, psoriasis and AD became prototype diseases driving the new pathogenesis-oriented dermatology. Identification of clinically relevant disease endotypes defined by objective biomarkers and/or image algorithms is the biggest current challenge on the way to true precision medicine in the field of inflammatory skin diseases.

Conflict of interest statement

The authors declare no conflict of interest related to this manuscript. K.E. is member of advisory boards and/or speaker for AbbVie, Boehringer Ingelheim, BMS, Janssen, LEO, Lilly, Novartis, Sanofi and UCB.

Author contribution

Alexander Schäbitz: Conceptualization (equal); Visualization (lead); Writing-original draft (supporting). **Kilian Eyerich:** Conceptualization (equal); Writing-original draft (equal). **Natalie Garzorz-Stark:** Conceptualization (equal); Supervision (equal); Writing-review & editing (equal).

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