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Editor's Summary

Discrimination That's Skin Deep

A molecular signature may be able to aid in the differential treatment of psoriasis from eczema. Quaranta *et al.* examined a group of individuals affected by both psoriasis and eczema and compared molecular signatures from psoriasis and eczema lesions on the same individual. This approach limited noise from interindividual variability, allowing the authors to focus on genes involved in disease pathogenesis. They found that psoriasis-specific genes involved not only immune mediators but also regulators of metabolism. In contrast, eczema-related genes included those related to the epidermal barrier and inflammasome activation. These insights provide not only new targets for disease-specific therapies but also an independently verified classifier that can be used in difficult to diagnose patients.

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PSORIASIS

Intraindividual genome expression analysis reveals a specific molecular signature of psoriasis and eczema

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Previous attempts to gain insight into the pathogenesis of psoriasis and eczema by comparing their molecular signatures were hampered by the high interindividual variability of those complex diseases. In patients affected by both psoriasis and nonatopic or atopic eczema simultaneously (n = 24), an intraindividual comparison of the molecular signatures of psoriasis and eczema identified genes and signaling pathways regulated in common and exclusive for each disease across all patients. Psoriasis-specific genes were important regulators of glucose and lipid metabolism, epidermal differentiation, as well as immune mediators of T helper 17 (T_H17) responses, interleukin-10 (IL-10) family cytokines, and IL-36. Genes in eczema related to epidermal barrier, reduced innate immunity, increased IL-6, and a T_H2 signature. Within eczema subtypes, a mutually exclusive regulation of epidermal differentiation genes was observed. Furthermore, only contact eczema was driven by inflammasome activation, apoptosis, and cellular adhesion. On the basis of this comprehensive picture of the pathogenesis of psoriasis and eczema, a disease classifier consisting of NOS2 and CCL27 was created. In an independent cohort of eczema (n = 28) and psoriasis patients (n = 25), respectively, this classifier diagnosed all patients correctly and also identified initially misdiagnosed or clinically undifferentiated patients.

INTRODUCTION

Psoriasis and eczema are prevalent inflammatory skin diseases with high individual disease burden and major socioeconomic impact (*1*, *2*). In recent years, numerous specific therapies were evaluated for both diseases. However, most clinical studies were empiric and not directly related to the increased basic knowledge of disease pathogenesis. Psoriasis and eczema respond differently, sometimes antipodally, to specific therapy regimes (*3*, *4*). Thus, a prerequisite for personalized medicine is a detailed understanding of the molecular mechanisms underlying both diseases.

Although basic knowledge of both conditions increased throughout recent years, our understanding of their molecular basis is still not complete. High-throughput techniques investigating the whole genome expression in biologic material such as microarrays are a useful tool to gain insight into pathogenesis (*5*–*7*). Of particular interest is a comparison of different inflammatory skin diseases, because it allows to distinguish commonly regulated genes involved in general cutaneous inflammation from genes that define the specific disease phenotype. However, previous attempts to use gene expression analysis for comparing psoriasis and atopic eczema were hampered by the high interindividual variability that is partially based on gender, age, and short-term environmental exposure before material sampling (*8*–*10*). In that context, patients affected by both psoriasis and eczema simultaneously (*11*) represent an excellent model to compare disease pathogenesis.

Here, we compare the molecular signature of psoriasis and eczema versus autologous noninvolved skin in 24 patients with coexisting diseases. By intraindividual disease comparison, disease-specific genes and signaling pathways become evident, resulting in a comprehensive picture of the pathogenesis of psoriasis and eczema.

Although it is possible to distinguish classical plaque-type psoriasis from typical atopic eczema, in daily clinical practice, discrimination is often challenging because psoriasis and eczema phenotypes might overlap or mimic each other. Therefore, we made use of our data set and defined a disease classifier consisting of two genes that accurately diagnosed either psoriasis or eczema, respectively, in an independent patient cohort (n = 53). Within this cohort, one initially misdiagnosed patient was identified and a clear prediction was given to a patient who was clinically and histologically unclear, which confirms the value of the disease classifier.

RESULTS

Principal components analysis

To investigate if a hypothesis-free analysis identifies clusters of psoriasis, eczema, and noninvolved skin, we performed a principal components analysis (PCA) on the full set of genes measured on the array. PCA has been chosen because of the good interpretability of results rather than using a nonlinear approach such as the nonlinear iterative partial least squares (NIPALS) algorithm or the t-distributed stochastic neighbor embedding (t-SNE). No clustering according to the disease was observed for psoriasis, eczema, and noninvolved skin (Fig. 1A). When the analysis was repeated on a nonsupervised hypothesis, a clustering of individual patients was observed (Fig. 1B). Thus, interindividual

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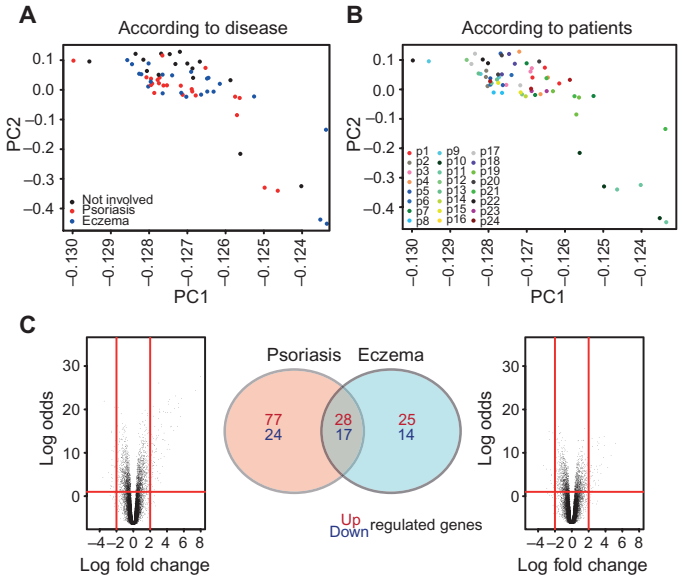

Fig. 1. Intraindividual comparison of gene expression in psoriasis and eczema. (**A** and **B**) PCA of all genes does not result in clustering according to the skin condition psoriasis (red bullets), eczema (blue bullets), or noninvolved skin (black bullets) (A), but rather in patient-wise clustering (B). (**C**) Number of genes significantly regulated compared to noninvolved skin in patients suffering from psoriasis and a variant of eczema simultaneously (n = 24), as illustrated using Venn diagrams and Volcano plots, respectively.

differences mask differences between the complex diseases psoriasis, eczema, and noninvolved skin. In contrast, when only genes significantly regulated compared to noninvolved skin were taken into account, a disease-related grouping was observed (fig. S1). This was expected because the genes are selected on the basis of significant disease-specific effects.

Intraindividual comparison of molecular signatures

We next evaluated the number of genes that were significantly differentially regulated in psoriatic and eczematous skin, respectively, compared to noninvolved skin in each patient. Numerous genes were regulated consistently among the 24 patients with coexisting psoriasis and either atopic, nonatopic, or contact eczema (Fig. 1C). One hundred one (77 up-regulated, 24 down-regulated) genes were exclusively expressed in psoriatic plaques, 39 (25 up-regulated, 14 down-regulated) genes were significantly regulated in eczematous but not psoriatic skin, and 45 (28 up-regulated, 17 down-regulated) genes were regulated in both diseases (Fig. 1C and table S3).

Function of significantly regulated genes

Genes significantly regulated in psoriatic and in eczematous skin compared to noninvolved skin were categorized into three groups: immune system, epidermal component, and metabolism. Table S1 lists all regulated genes including P values.

Concerning the immune system, differences between psoriasis and eczema were observed: exclusively in psoriatic skin, cytokines belonging to the interleukin-10 (IL-10) family such as IL-19 and IL-20, as well as IL-36A and IL-36G, were significantly up-regulated (Fig. 2). A nonsignificant trend for a higher induction of T helper 17 (T_H17)–associated cytokines IL-17A, IL-17F, IL-21, and IL-22 was also observed

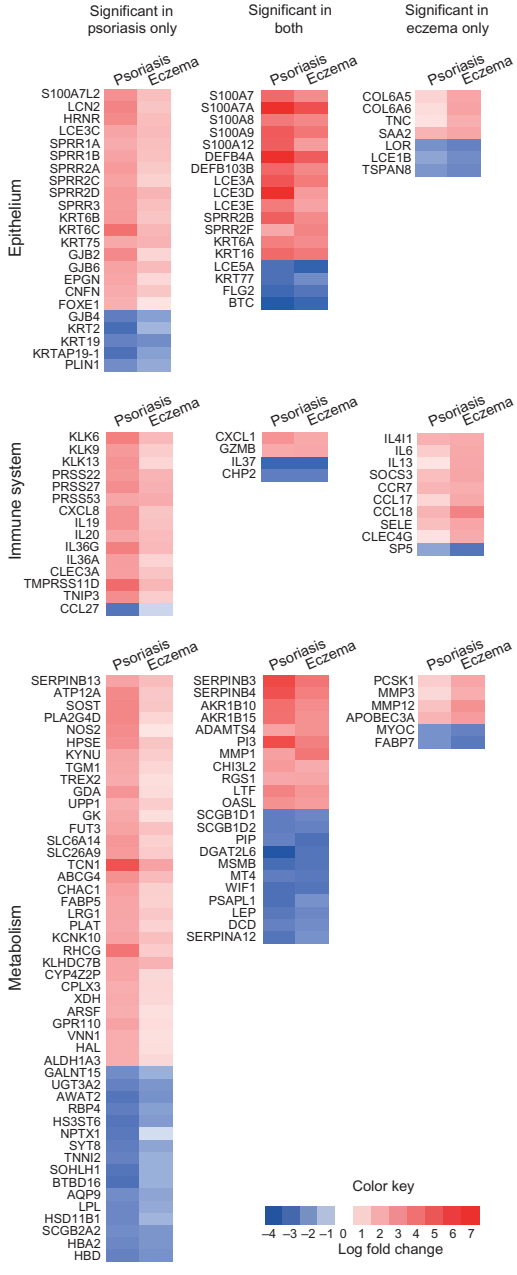

Fig. 2. Regulated genes in psoriasis and/or eczema. Heat map of all genes significantly regulated in psoriasis (left side) and eczema (right side) within the same patients compared to autologous noninvolved skin reveals clusters of genes regulated exclusively in psoriasis and in eczema. The histogram gives the color code for the $\log_2$ fold induction.

in psoriatic plaques. Cytokines that were exclusively induced in eczematous lesions were IL-6 and the T_H2 cytokine IL-13 (Fig. 2), with a trend for a higher induction of other T_H2 cytokines IL-4, IL-5, and IL-10 in eczematous compared to psoriatic skin (table S1).

The chemokines CCL17 and CCL18 were up-regulated in eczematous lesions to a higher degree than in psoriatic skin. CCL27 was down-regulated significantly in psoriatic skin. On the other hand, CXCL1 and CXCL8 (IL-8) showed a stronger up-regulation in

psoriatic plaques, with CXCL8 being exclusively regulated in psoriatic skin (Fig. 2).

Bridging the immune system and the epidermal component, numerous antimicrobial peptides (AMPs) were found to be up-regulated in both psoriatic and eczematous skin compared to noninvolved skin, respectively. The defensin members DEFB4 and DEFB103B, as well as the S100 proteins S100A7A, S100A7, S100A8, S100A9, and S100A12, were significantly up-regulated in both diseases. However, induction of all detected AMPs was much higher in psoriatic than in eczematous skin. Accordingly, the IL-20–induced kallikrein-related peptidases KLK6, KLK9, and KLK13, demonstrated to induce AMPs, were exclusively up-regulated in psoriatic but not in eczematous skin (Fig. 2).

Differences were also observed regarding early differentiation markers of the small proline-rich protein (SPRR) family and the late cornified envelope (LCE) family. SPRR1A, SPRR1B, SPRR2A, SPRR2B, SPRR2C, SPRR2D, LCE3C, and *cornifelin* were exclusively up-regulated in psoriatic plaques. LCE3A, LCE3D, and LCE3E were up-regulated in both psoriasis and eczema skin, but to a higher degree in psoriasis. In contrast, LCE1B and LCE5A were down-regulated in both psoriatic and eczematous skin, but to a higher degree in eczema. A heterogeneous picture was observed regarding keratin regulation, with KRT6A, KRT6B, KRT6C, KRT16, and KRT75 highly up-regulated in psoriatic skin and KRT2, KRT19, and KRT77 down-regulated more in psoriatic than in eczematous skin. The late differentiation genes of the *filaggrin* family FLG and FLG2 were also down-regulated in both psoriatic and eczematous skin. *Hornerin* was up-regulated more in psoriatic than in eczematous compared to noninvolved skin (Fig. 2).

Numerous genes involved in glucose, lipid, and amino acid metabolism were exclusively regulated in psoriatic, but not in eczematous skin. Namely, regulation of the phospholipase PLA2G4D, nitric oxide synthase 2 (iNOS or NOS2), adenosine triphosphate (ATP)–binding cassette ABCG4, serine proteases (PRSS22, PRSS27, and PRSS53), *kynureninase*, *transcobalamin*, and the Wnt signaling inhibitor *sclerostin* were up-regulated exclusively in psoriatic plaques. The aldo-keto reductase family members AKR1B15 and AKR1B10 and the peptidase inhibitor PI3 were up-regulated in both psoriatic and eczematous skin, but more in psoriasis (Fig. 2).

Distinct and common signaling pathways

The differential regulation of single genes in psoriatic and eczematous skin was reflected by corresponding pathways (Fig. 3 and table S2). The Gene Ontology (GO) annotations revealed several commonly regulated immune pathways such as "innate immune response," "leukocyte cell-cell adhesion," "defense response to bacteria," "defense response to fungi," "cytokine activity," and "chemokine activity." The main immune pathways were also significant when only genes regulated in either psoriasis or eczema were investigated, indicating that different signaling cascades within one GO term were induced (Fig. 3).

This was also observed for GO terms regarding the epidermal compartment, where the pathways "keratinization" and "cornified envelope" showed significance for both psoriatic and eczematous skin independently of each other, indicating that those pathways result from a different gene profile between psoriasis and eczema.

Pathways that were observed exclusively in psoriatic skin related to the epidermal compartment and to metabolism. Among the most significant hits were "positive regulation of epidermis development," "gap junction channel activity," "connexon complex," "peptide cross-linking," and "serine-type endopeptidase activity" (Fig. 3).

Heterogeneity of eczema patients

To understand whether the observed differences of psoriasis and eczema were a general phenomenon spanning all clinical variants of eczema, a subtype analysis of naturally occurring versus induced eczema [allergic contact dermatitis (ACD)] was performed.

In general, variability in the ACD group was smaller compared to naturally occurring eczema, with 172 genes regulated exclusively

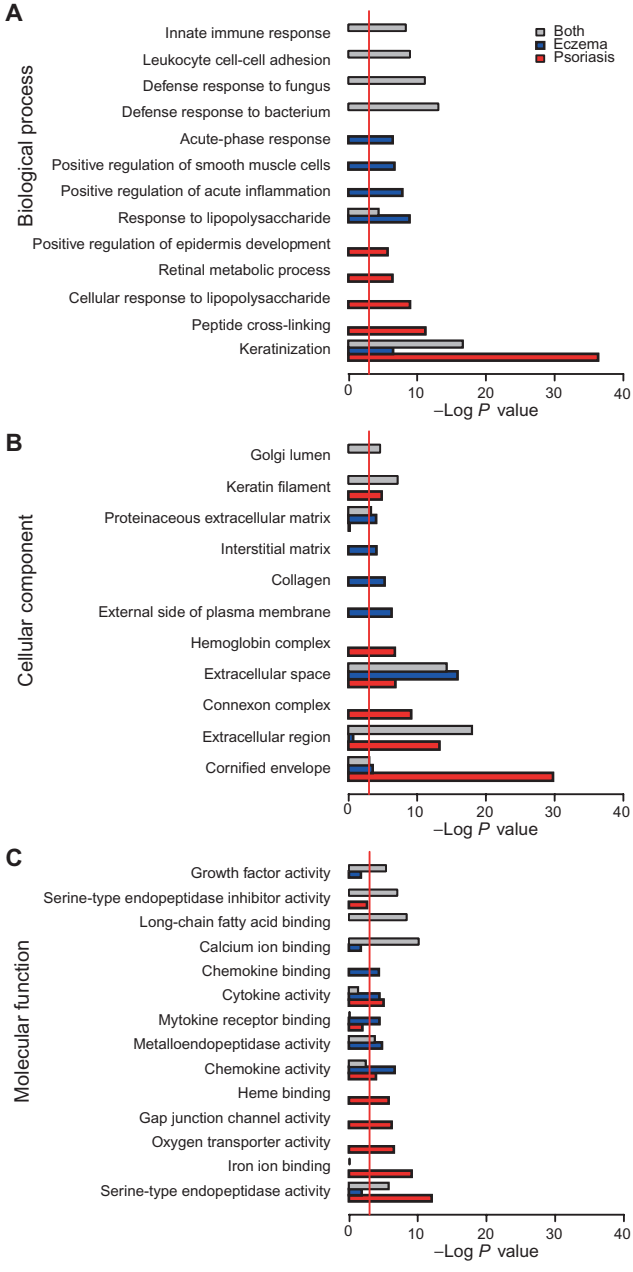

Fig. 3. Signaling pathway analysis of psoriasis and eczema. (**A** to **C**) Most significant hits for the GO terms "biological process" (A), "cellular component" (B), and "molecular function" (C) for genes regulated consistently in psoriasis and eczema (gray bars) as well as exclusively in psoriasis (red bars) or eczema (blue bars), respectively. The bar size indicates the level of significance for each pathway (negative log *P* value); the vertical line shows the 0.05 significance level.

in ACD (90 up-regulated, 82 down-regulated), but not in naturally occurring eczema compared to noninvolved skin. Twenty-eight genes were regulated only in naturally occurring eczema (22 up-regulated, 6 down-regulated), and 33 genes were regulated in common (27 up-regulated, 6 down-regulated; Fig. 4A).

Although the epithelial antimicrobial response was similar in both naturally occurring and ACD, marked differences were observed regarding epidermal differentiation. Early differentiation markers of the SPRR family and late differentiation markers of the LCE3 family were up-regulated only in naturally occurring eczema. In contrast, late differentiation markers of the LCE1 and LCE2 family were strongly down-regulated exclusively in ACD. Extracellular matrix proteins such as HAS3 and EPSTI1 as well as numerous cell-cell adhesion molecules such as ICAM-1 were exclusively up-regulated in ACD (Fig. 4B and table S3).

Furthermore, an acute immune response was observed more in ACD than in naturally occurring eczema. Members of the inflammasome such as IL-1β and AIM2 as well as numerous chemokines including the neutrophil-attracting CXCL8 or the T_H1-associated CXCL9, CXCL10, and CXCL11 were exclusively up-regulated in ACD reactions.

In line with the identified top hits, immune pathways were significant in both eczema subtypes, with more hits in ACD than in naturally occurring eczema. In contrast, the GO term cornified envelope was identified within the naturally occurring eczema lesions only (Fig. 4C and table S4).

Within the well-defined and controllable system of ACD, variability of gene regulation was low. Here, two initially screened patients with false-positive reactions could be excluded on the basis of consistency (table S5). When those two patients were carefully evaluated, one patient turned out to have a negative patch test result, and the other patient had a severe irritant reaction spanning the psoriasis and the eczema field (fig. S2).

Establishing a disease classifier to distinguish psoriasis and eczema

Because differences between psoriasis and eczema were observed at both single-gene and signaling pathway level, we sought to translate these basic results into a disease classifier that enables to distinguish psoriasis from eczema. Fifteen genes that were selected according to the degree of significantly different expression in the microarrays throughout all patients (Table 1 and Fig. 5A) were included in an independent cohort with 19 patients (9 for psoriasis, 10 for eczema) to train a classifier. Expression of the selected 15 genes was detected using real-time polymerase chain reaction (PCR) in all 19 patients, and a two-sample, two-sided Welch's *t* test on the log-transformed

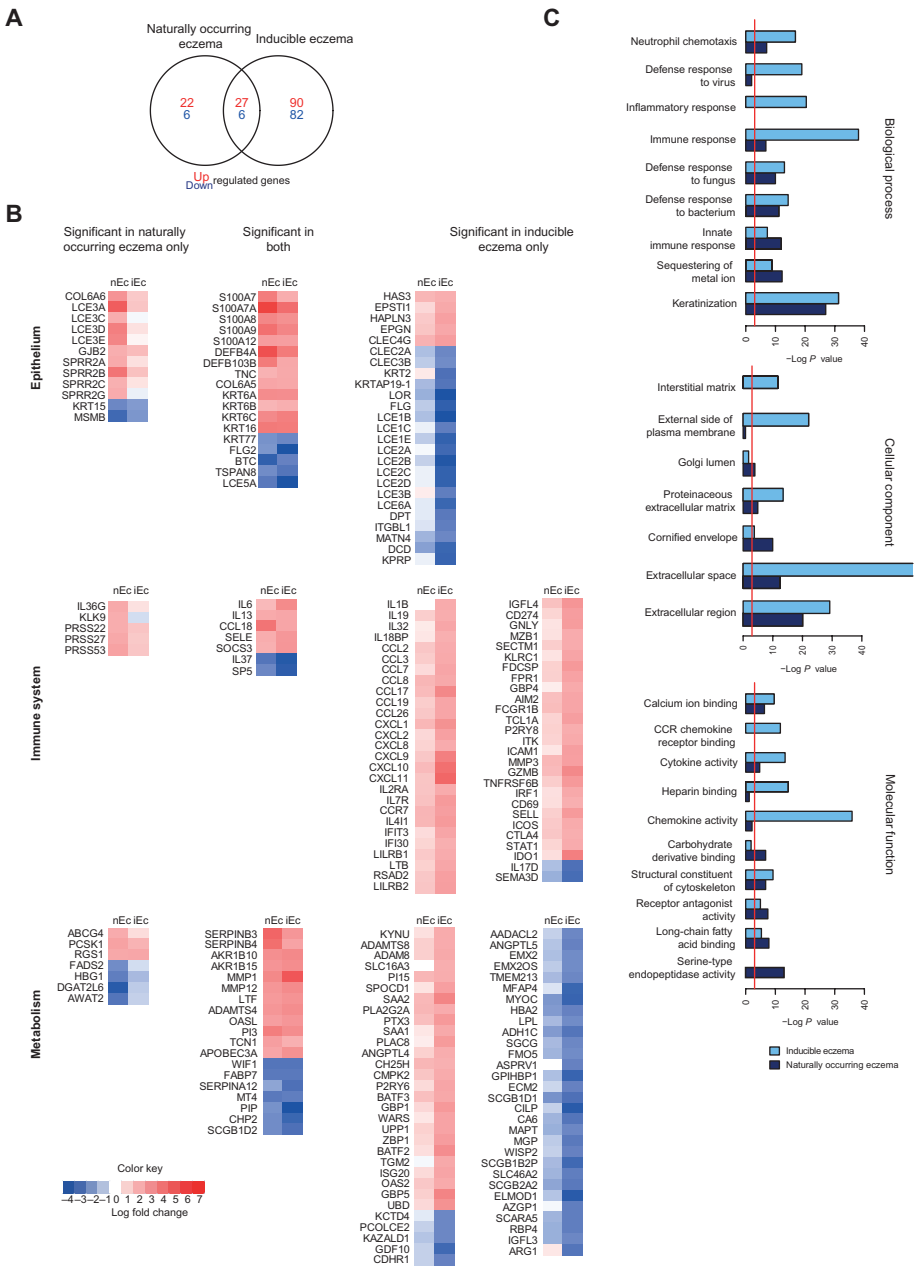

Fig. 4. The heterogeneity of eczema. (**A**) Venn diagrams showing genes regulated in common versus exclusive in naturally occurring eczema (nEc: atopic eczema, $n = 6$, and nummular or dyshidrotic eczema, $n = 7$) and induced eczema (iEc: ACD, $n = 11$). (**B**) Heat map of all genes significantly regulated in naturally occurring eczema (left side) and eczema (right side) within the same patients compared to autologous noninvolved skin reveals gene clusters of genes regulated exclusively in naturally occurring eczema as well as in induced eczema. The histogram gives the color code for the $\log_2$ fold induction. (**C**) Signaling pathway analysis of naturally occurring and induced eczema. Shown are the most significant hits for the GO terms biological process, cellular component, and molecular function for genes regulated exclusively in naturally occurring (dark blue bars) or induced eczema (light blue bars), respectively. The bar size indicates the level of significance for each pathway (negative log *P* value); the vertical line shows the 0.05 significance level.

measurements followed by a Bonferroni *P* value correction was used to assign each of the 15 genes with a *P* value. The primer sequences used for real-time PCR are given in table S4. CCL27 and NOS2 were the genes with lowest adjusted *P* values (for significant up- and down-regulation, respectively, of psoriasis versus eczema). On the basis of these two genes, a classifier was trained using a 10-fold cross-validation and support vector machines (SVMs). An average accuracy of 100% was achieved (Fig. 5B). With an independent third cohort (34 patients in total; 16 psoriasis patients and 18 eczema patients), the classifier was tested and could classify 33 of 34 patients as predicted from clinical and histological evaluation ($\kappa = 0.94$; Fig. 5C). Prediction probabilities of the patients are listed in table S7.

One patient was classified as having eczema with a probability of 0.85, although the given diagnosis was psoriasis. Back-tracing clinical and histological features of this patient revealed that the initial diagnosis psoriasis was most likely not correct. The 54-year-old patient presented with disseminated, demarcated eczema-like skin lesions with centripedal desquamation that had erupted 2 months before (fig. S3, A to C). Histological evaluation revealed neutrophil microabscesses, spongiosis, single-cell necrosis in the epidermis, and an epidermotropism of immune cells (fig. S3, D and E). Other hallmarks for psoriasis such as acanthosis and epidermal thinning above dermal papillae containing dilated and tortuous capillaries were not observed. In line with that observation, the patient did not respond well to dithranol. Furthermore, skin lesions did not relapse after remission. Retrospectively, other diagnoses like pityriasis rosea, eczema, or pityriasis lichenoides chronica are clearly to be favored in this patient.

Besides patients with a given diagnosis from clinical and histological evaluation, one patient was tested where the gold standard methods could not distinguish between psoriasis and eczema (Fig. 5D). The 53-year-old female patient suffered from inflammatory skin lesions since years. Eczema could have been favored because she suffered from allergic asthma, her immunoglobulin E was mildly elevated (108 IU/ml), and the lesions were itchy; the positive family history for psoriasis and the very stationary plaques in predilection areas were typical rather for psoriasis. Also, the histological evaluation was conflicting, with a plump acanthosis, partially missing stratum granulosum, and parakeratosis accounting for psoriasis. On the other hand, T cell epidermotropism and very few neutrophils with missing microabscesses were more typical for eczema. When this patient was tested in the classifier, the two biopsies were classified as eczema with a probability greater than 99%, indicating that the classifier might be useful even in cases where established gold standard diagnostic tools fail.

DISCUSSION

Psoriasis and eczema are complex inflammatory skin diseases driven by genetic background, altered immune responses, and environmental influences. By comparing gene expression in lesional skin of both conditions, general cutaneous inflammation can be distinguished from disease-specific genes regulated in one of the two conditions. Previous attempts to compare psoriasis and eczema have been made with different and partially inconsistent results (*8*–*10*, *12*, *13*). This study rules out any interindividual differences by comparing psoriasis and eczema lesions within the same patients. Thus, a difference to previous studies is that all observed regulated genes are not driven by the genetic

Table 1. Fifteen genes that distinguished psoriasis and eczema in all three cohorts tested (*n* = 53 in total). Genes that build up the disease classifier are in bold font. Given are the full names, main functions, and a grouping into metabolism, immune system, and epidermis. Note that this is a rough grouping because genes involved in metabolism may also affect the immune system.

Target	Full name	Function	Category
SOST	*Sclerostin*	Inhibition of Wnt signaling	Metabolism
PLA2G4D	*Phospholipase A2, group IVG*	Widespread metabolic functions	Metabolism
IL36G	*Interleukin-36G*	Induces epidermal proliferation and AMPs	Immune system
NOS2	***Inducible nitric oxide synthase 2***	**Stress-induced molecule with multiple functions on immune and metabolic processes**	**Metabolism, immune system**
KLK13	*Kallikrein-related peptidase 13*	Induction of AMPs in the skin	Immune system
GDA	*Guanine deaminase*	Involved in purine metabolism	Metabolism
IL36A	*Interleukin-36A*	Induces epidermal proliferation and AMPs	Immune system
TGM1	*Transglutaminase 1*	Formation of the cornified envelope	Epidermis
NPTX1	*Neuronal pentraxin 1*	Involved in neuronal metabolism and damage	Metabolism
CCL27	***Chemokine (C-C motif) ligand 27***	**Binds to CCR10, promotes lymphocyte migration into the skin**	**Epidermis, immune system**
CLEC4G	*C-type lectin family member 4*	Inhibits activation of $CD4^+$ T cells	Immune system
IL13	*Interleukin-13*	Acts on epithelium (inhibition of AMPs, induction of fibrosis, induction of chemokines) and on macrophages	Immune system
TCN1	*Transcobalamin1*	Vitamin B12 binding	Metabolism
TMPRSS11D	*Serine transmembrane protease 11D*	Preform of macrophage activating molecule	Immune system
RHCG	*RH family, C glycoprotein*	Ammonia transporter	Metabolism

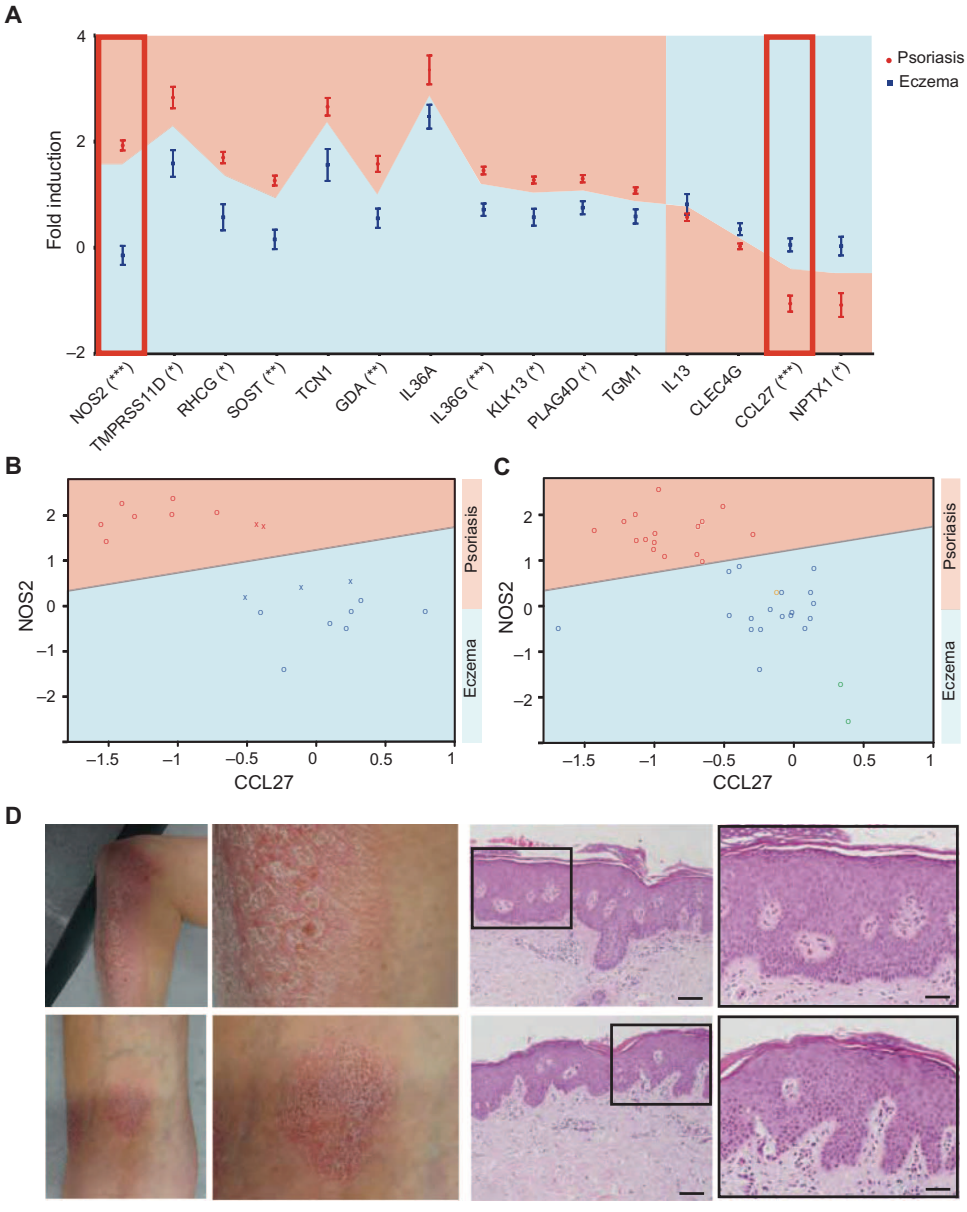

Fig. 5. Establishing a disease classifier to distinguish psoriasis and eczema. (**A**) Real-time PCR validation of 15 genes significantly different between psoriasis (n = 9) and eczema (n = 10). The curve shows the cutoff values between the two groups for each gene. Red frames indicate the two genes chosen to build up the disease classifier. *P < 0.05; **P < 0.01; ***P < 0.001; no asterisk, P < 0.1 (Bonferroni-corrected for multiple testing). (**B**) A disease classifier consisting of NOS2 (y axis) and CCL27 (x axis) accurately separates psoriasis and eczema patients in a training set consisting of 19 patients [see (A): 9 psoriasis, 10 eczema]. Shown are data samples of the training set after log transformation and scaling. The crosses indicate the support vectors; the circles indicate the remaining data samples of the training set. (**C**) Performance of the disease classifier in an independent test cohort (16 psoriasis patients, 18 eczema patients). (**D**) The yellow circle shows one initially misclassified patient; the green circles show the clinically and histologically unclear patient. Scale bars, 100 μm (overview) and 50 μm (insets).

background but depend exclusively on the local stimulus that creates a microenvironment, leading to the clinical phenotype psoriasis or eczema, respectively.

Ruling out such interindividual variability, psoriasis and eczema as well as noninvolved skin do not cluster according to the skin condition, but rather, a nonsupervised PCA results in patient-wise clustering. This fact highlights the importance of interindividual differences and confirms the value of our system. This picture changes when only genes significantly regulated in diseases compared to noninvolved skin are taken into account. In this case, a disease-related grouping is observed.

A second important difference to previous studies is that all clinical variants of eczema are covered in the present investigation. Eczematous diseases are categorized into "atopic eczema," "contact dermatitis," and "other dermatitis" such as nummular dermatitis or dyshidrotic eczema (*14*). These variants of eczema show differences regarding kinetics, time course, and immune infiltrate. Those differences are reflected by the molecular changes in lesional skin. We demonstrate here that self-limited, acute eczematous reactions such as ACD to nickel are mostly driven by a broad immune response including inflammasome activation, cell-cell adhesion, and apoptosis. Furthermore, extracellular matrix proteins are induced. The fact that more genes are significantly regulated in the ACD group also reflects that it is easier to sample skin biopsies at the same stage of the disease in this well-defined model than in naturally occurring eczema. These observations are in line with the literature (*15*). We observed a mutually exclusive pattern of epidermal differentiation in ACD and naturally occurring eczema, with the latter showing a broad up-regulation of early and late differentiation markers, whereas in ACD distinct differentiation markers are generally down-regulated. Further investigations with larger cohorts are required to compare all eczema subtypes in more detail. Nevertheless, all clinical variants of eczema are clinically and histologically similar (*11*, *16*, *17*). Thus, for the clinician, a general statement on differences between psoriasis and all eczema variants is of high value and was the aim of this study.

As expected, genome-wide expression analysis of both psoriasis and eczema involves mainly the immune system and epidermal components (Fig. 6). A marked difference between psoriasis and eczema is observed regarding the epidermal integrity. Whereas eczema reactions are accompanied by severe defects in epidermal cornification and barrier function, psoriasis is characterized by disturbed epidermal development and differentiation. Namely, multiple epidermal differentiation complex (EDC) genes of the SPRR (*18*) family and the LCE family are expressed significantly higher in psoriasis. LCE

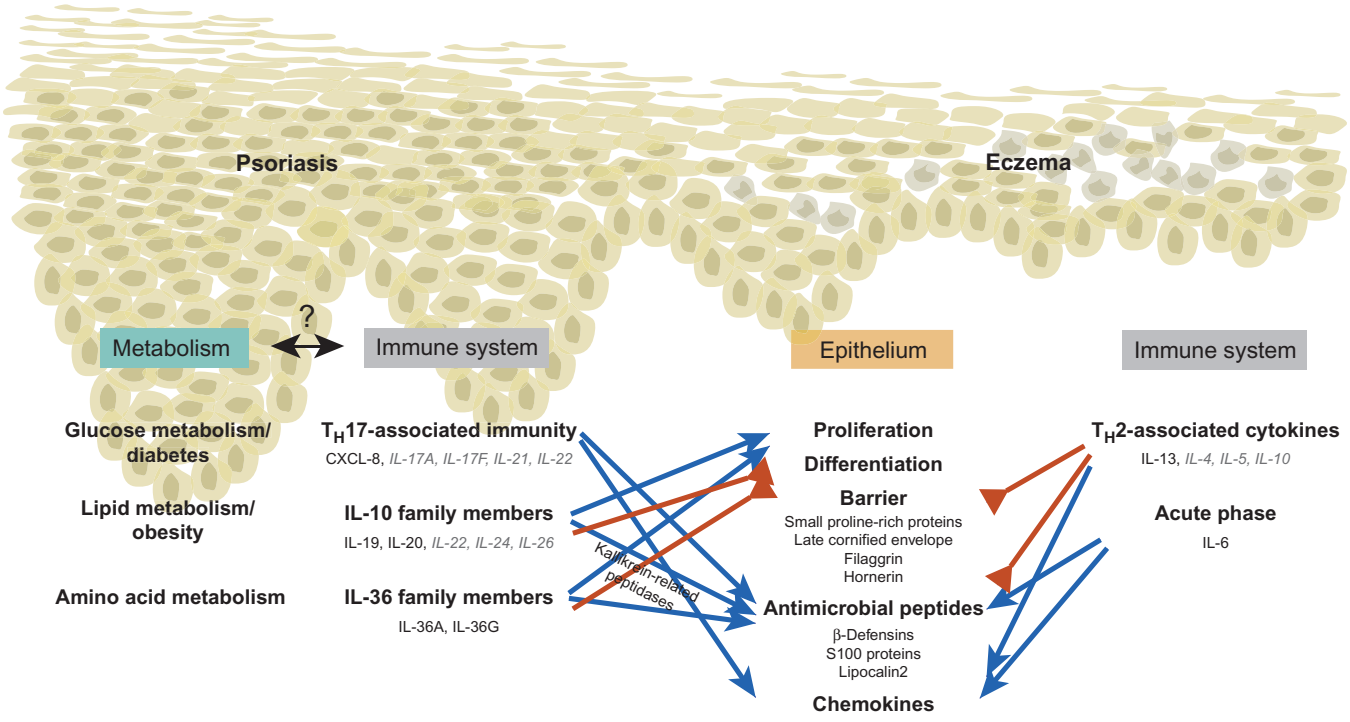

Fig. 6. A comprehensive view on the pathogenesis of psoriasis and eczema based on intraindividual comparison of molecular signatures. Named genes are significantly regulated exclusively in psoriasis or eczema; genes in italic show a nonsignificant trend of differences. Blue arrows indicate induction; red arrows indicate inhibition.

genes are induced by iatrogenic skin barrier disruption and were previously reported to be associated with psoriasis (*19*), but not with atopic eczema (*20*). Our data confirm and expand a recent genomic expression comparison of psoriasis and atopic eczema that reports a disease-specific broad cornification defect in atopic eczema (*12*). Besides SPRR and LCE genes, the EDC genes *filaggrin* and *hornerin* are differently expressed: *filaggrin* is down-regulated in both psoriasis and eczema, whereas *hornerin* is up-regulated in psoriasis. This supports the concept that dysfunctional *filaggrin* predisposes to atopic eczema (*21*), whereas *hornerin* is associated with epithelialization after wounding and was previously found to be expressed in psoriasis lesions (*22*).

Increasing evidence suggests that the immune system directly regulates both epidermal barrier disruption and regeneration. Genes exclusively induced in psoriasis involve the IL-10 family members IL-19 and IL-20 that induce epidermal regeneration and differentiation (*23*), as well as IL-36A and IL-36G that are functionally similar to T_H17 cytokines and induce a psoriasis-like epidermal phenotype in mice (*24*). A trend for higher induction of the T_H17 cytokines IL-21 (*25*) and IL-22 (*26*) inducing a similar epidermal phenotype is also evident in psoriasis. Together, this cytokine network induces epidermal metabolism and proliferation and inhibits its differentiation, indicating a crosstalk between the epidermal compartment and the immune system that results in a wound healing–like reaction in psoriasis.

On the other hand, we demonstrate that all clinical variants of eczema share a significantly higher induction of the T_H2 cytokine IL-13, with a trend for a higher expression of other T_H2 cytokines such as IL-4, IL-5, and IL-10 compared to psoriasis. T_H2 cytokines down-regulate genes of the EDC (*11*, *27*, *28*) and the induction of AMPs in the skin (*29*, *30*). Thus, they oppose T_H17 and IL-10 family cytokines that induce AMPs via kallikrein-related peptidases (*31*) and are higher expressed in psoriasis. In line with those results and confirming previous studies, eczema is characterized by a significantly lower expression of AMPs of the β-defensin and S100 families (*32*) as well as the neutrophil-associated AMP *lipocalin2*, previously reported as a marker to distinguish psoriasis from atopic eczema (*13*). This might partially explain why the skin of almost all eczema patients is colonized by *Staphylococcus aureus* (*1*). However, even if to a lesser degree than in psoriasis, AMPs are up-regulated in eczema compared to healthy skin (*33*), indicating heterogeneous immune signals in eczema skin. A proinflammatory marker with impact on innate immunity that is significantly higher expressed in eczema is IL-6. A pathogenic role for IL-6 in eczema is likely because patients respond to its therapeutic neutralization (*34*). The concept that AMP induction is at least partially driven by the immune system is supported by the fact that AMPs are induced similarly in healthy, psoriasis, and eczema skin upon iatrogenic barrier disruption, but quantitative differences are observed in psoriasis plaques and eczema lesions, respectively (*35*).

Another marked difference between psoriasis and eczema is intensive up-regulation of genes involved in metabolism in psoriasis. Among them are genes regulating glucose metabolism/insulin resistance and lipid metabolism/obesity such as aldo-keto reductases (*36*), phospholipases (*37*), proteases (*38*), iNOS (NOS2) (*39*), and ATP-binding cassette proteins (*40*). The Wnt inhibitor sclerostin is also highly up-regulated in psoriasis plaques. Emerging evidence suggests the Wnt/β-catenin pathway to link diabetes, obesity, and psoriasis (*41*, *42*). A recent investigation of the psoriasis transcriptome in a large cohort also observed up-regulation of genes associated to metabolism (*7*). This observation might explain the clinical association of psoriasis with metabolic syndrome

and cardiovascular diseases (*43*, *44*). It might be speculated that the psoriasis-immune profile influences metabolism; however, this hypothesis remains to be investigated.

This study is limited by the size and nature of the patient's cohort. In our experimental setting, genetic differences are not taken into account. Furthermore, patients with coexisting psoriasis and eczema are rare, and material sampling critically depends on an experienced clinician. To ensure the clinical diagnoses, we investigated all biopsies histologically. Nevertheless, a final proof that our patients do develop typical psoriasis and eczema lesions, respectively, cannot be given. Besides clinical and histological investigation, the good consistency of top hit regulated genes of our analysis and large psoriasis cohorts (*6*, *7*) gives evidence that our data can be transferred to psoriasis and eczema patients in general.

The comprehensive comparative analysis performed in this study confirms that psoriasis and eczema are driven by distinct immune responses (Fig. 5). In psoriasis, functionally overlapping T_H17 responses, IL-10 family cytokines such as IL-19 and IL-20, as well as IL-36 signatures are dominant. All those immune responses induce a wound healing–like reaction with induction of epidermal metabolism and innate immunity. Psoriasis is also associated with numerous metabolic processes central for glucose, lipid, and amino acid metabolism. Thus, psoriasis is not only an inflammatory but also a metabolic disease. Whether metabolic processes are influenced by the immune system remains to be investigated. On the other hand, all chronic variants of eczema share a severe defect in epidermal cornification and barrier as well as decreased innate epidermal immunity that is at least partially controlled by T_H2 immune responses.

In daily clinical practice, it is often difficult to distinguish certain variants of psoriasis and eczema. This holds especially true for skin lesions of palmae or scalp and for psoriasis mechanically altered by scratching. On the basis of the comprehensive pathogenesis analysis of this study, we designed a disease classifier consisting of two genes (NOS2 and CCL27) to distinguish general forms of psoriasis and eczema. Those genes were chosen because they show a strong diversity between psoriasis and eczema in all investigated patients and they are opposing in terms of regulation compared to noninvolved skin. Furthermore, they summarize functional differences of psoriasis and eczema because NOS2 is both critical for numerous metabolic processes (*45*) and involved in T_H1 and T_H17 immunity (*46*), and CCL27 combines chemoattractive properties with regulation of epidermal development (*47*). The classifier identifies the correct diagnosis with a high accuracy, and our initial results suggest that it might be superior to gold standard techniques such as clinical evaluation and histology. Classifiers were suggested recently (*12*), but the one presented here is smaller and the first that is validated in independent disease cohorts at the level of real-time PCR. Because therapeutic strategies for psoriasis and eczema are distinct and sometimes opposing, this diagnostic tool could be valuable to set the correct diagnosis in special cases.

MATERIALS AND METHODS

Study design

This study was designed as a nonblinded proof-of-concept study to investigate the molecular signature of psoriasis and eczema, respectively. Inclusion criteria were adult (age ranging from 18 to 60 years) patients with a confirmed diagnosis of chronic plaque-type psoriasis [Psoriasis Area Severity Index (PASI) >10] and of eczema for at least 6 months before biopsy sampling. Exclusion criteria were treatment with immune-efficient medication before material sampling (washout phase 6 weeks for systemic, 2 weeks for local treatment). Diagnoses were made according to clinical and histological criteria as published previously (*11*). Clinical evaluation of the patients was quantified using the SCORAD and the PASI system, respectively, and the intensity of induced contact dermatitis reactions to nickel was documented according to guidelines as published previously (*11*). Patients with coexisting plaque-type psoriasis and naturally occurring eczema (atopic eczema, $n = 6$; nummular or dyshidrotic eczema, $n = 7$) as well plaque-type psoriasis patients with type IV sensitizations to nickel (ACD, $n = 11$; induced eczema) build up the first cohort. Mean age of patients was 45 ± 11 years, 33% of patients were male, all were Caucasians, 40% were smokers, and mean body mass index was 22.4 ± 4.8. All patients gave their written consent to participate in the study, and the study was approved by the local ethical committee.

Skin punch biopsies (6 mm) were obtained under local anesthesia from one eczema lesion, one psoriasis plaque, and clinically noninvolved skin of all patients. Biopsies were divided for routine histologic evaluation and isolation of total RNA, respectively.

The cohort for the validation of the disease classifier consisted of patients with psoriasis ($n = 25$, 41% male, mean age 47 ± 13 years) and patients with eczema ($n = 28$, 38% male, mean age 35 ± 15 years). Again, diagnosis was made upon clinical and histological appearance, and patients gave their written informed consent to participate in the study. Figure S4 shows a flow chart illustrating the different cohorts for microarray data, classifier training, and classifier testing.

Isolation of total RNA from skin biopsies

Skin tissue specimens were stored in PAXgene Tissue Containers (Qiagen) until isolation of total RNA with the PAXgene Tissue RNA Kit (Qiagen), according to the manufacturer's protocol. The RNA yield and quality were determined with a NanoDrop ND1000 UV-Vis Spectrophotometer and the 2100 Bioanalyzer (Agilent), respectively. Complementary DNA (cDNA) was synthesized from 500 ng of total RNA and transcribed using the High Capacity cDNA Reverse Transcription Amplification Kit (Applied Biosystems) according to the manufacturer's instructions.

Whole-genome expression arrays

Complementary RNA was synthesized from 25 ng of total RNA and transcribed using the High Capacity cDNA Reverse Transcription Amplification Kit (Applied Biosystems) according to the manufacturer's instructions. Samples were amplified and Cy3-labeled using the Agilent Low Input Quick Amp Labeling Kit (Agilent Technologies) according to the manufacturer's instructions and hybridized to a SurePrint G3 Human GE 8X60K BeadChip (Agilent Technologies). After washing the hybridized arrays, fluorescence signals were detected by reading the arrays in the microarray scanner system iScan (Agilent Technology). The Agilent Feature Extraction software was used to read and process microarray image files.

Classifier buildup

Genes that were significantly regulated in either psoriasis or eczema, but not the corresponding disease, were screened for inclusion into the disease classifier. Subsequently, 15 marker genes were selected according to the following criteria: genes with most predominant difference between psoriasis and eczema, and functional annotation as epidermal, immune-related, and metabolic genes.

Primer design and real-time PCR

Primers amplifying genes of interest were designed using the publicly accessible Primer3 software (http://frodo.wi.mit.edu/primer3/). A list of used primers is shown in table S6.

Real-time PCRs were performed in 384-well plates using the Fast Start SYBR Green Master Mix (Roche Applied Science) and the ViiA 7 Real Time PCR machine (Applied Biosystems). The expression of transcripts was normalized to expression of 18*S* ribosomal RNA as a housekeeping gene. Data were expressed as mRNA fold change relative to noninvolved skin as calibrator. Relative quantification (RQ) was determined according to the following formula: $RQ = 2^{-\Delta Ct}$.

Statistics microarray analysis

For statistical analysis of microarray data, R software (http://www.r-project.org) and the limma package from Bioconductor (http://www.bioconductor.org) were used. First, raw data were background-corrected using the "normexp" method and then normalized with the "cyclic loess" approach. Next, control probes and low expressed probes with normalized signal intensities less than 10% of the 95 percentile of the negative controls of each array were filtered out. Within-array replicates for each gene were averaged. Log_2 fold change of the paired samples was computed for each diseased sample against the corresponding noninvolved skin sample. A fixed-effects linear model was fit for each individual gene to estimate expression differences between the compared groups of samples. Empirical Bayes approach was used to moderate the SEs of the normalized log_2 fold changes. Finally, two-sided moderated paired *t*-statistics and log-odds of differential expression (*B* statistics) and raw and adjusted *P* values (false discovery rate) controlled by Benjamini-Hochberg (*48*) were computed to identify genes that are differentially expressed between the different disease groups. Genes with an absolute log_2 fold change larger than 2 and a corrected *P* value smaller than the testing level (α) of 0.05 were defined as significantly differentially expressed hits. The microarray data are available in the Gene Expression Omnibus database (GSE57225).

PCA was done on the normalized and sample-averaged gene expression data of each array (*49*).

For the enrichment analysis, the "topGO" package from Bioconductor using the "weight01" method (*50*) was used on (i) the hit genes that were significantly differentially regulated in psoriasis but nonregulated in the all eczema samples (psoriasis), (i) the hit genes that were significantly differentially regulated in the all eczema samples but nonregulated in psoriasis (all eczema), and (iii) the hit genes that were significantly differentially regulated in both psoriasis and eczema samples compared to noninvolved skin (both). For the analysis of the real-time PCR data, the R software was used. To train the classifier, we applied the R package "e1071" (http://CRAN.R-project.org/package=e1071) using SVMs on a second independent cohort ($n = 19$). To get normally distributed data, the measurements of the selected 15 genes were transformed using the logarithm to the base 10. We tested for normality using Shapiro-Wilk normality test ($P = 0.05$). Then, a two-sample, two-sided Welch's *t* test followed by a Bonferroni *P* value correction was used to test for differential expression. The two genes that were most significantly down-regulated (CCL27, adjusted $P = 5.31 \times 10^{-4}$) or up-regulated (NOS2, adjusted $P = 1.53 \times 10^{-6}$) were selected for the classifier. The scaled and log-transformed data of the two genes were used as a training set for a *C*-classification using a linear kernel function with $C = 1$. To train the classifier, a 10-fold cross-validation was used. Then, the classifier was tested on log-transformed data samples of a third independent cohort ($n = 34$) by predicting the disease class and computing probability predictions based on the trained model.

SUPPLEMENTARY MATERIALS

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Fig. S1. Clustering analysis of significantly regulated genes results in grouping of the diseases.
Fig. S2. Identification of two false-positive patch test results in the induced eczema cohort based on gene regulation consistency.
Fig. S3. Clinical and histological presentation of a patient initially misdiagnosed as psoriasis as detected by the disease classifier.
Fig. S4. Flow chart of patient cohorts used for microarray data, classifier training, and classifier testing.
Table S1. Top hit list of genes regulated in both psoriasis and eczema as well as of exclusively regulated genes.
Table S2. Raw data of pathway analysis in psoriasis and eczema as shown in Fig. 3.
Table S3. Top hit list of genes regulated both in eczema subtypes and exclusively in induced or naturally occurring eczema.
Table S4. Raw data of pathway analysis in eczema subtypes as shown in Fig. 4.
Table S5. Identification of two false-positive patch test results in the induced eczema cohort based on gene regulation consistency.
Table S6. Primers used for validation of disease classifier.
Table S7. Probabilities of the patients in the independent test cohort for the diagnosis of psoriasis or eczema according to the disease classifier ($n = 34$ plus unclear case as indicated below).

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