Montagna Symposium on the Biology of Skin

Profiling Immune Expression to Consider Repurposing Therapeutics for the Ichthyoses

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Despite extensive discovery about the mutations underlying genetic skin disorders, there have been few therapeutic advances. Better understanding of the molecular changes that may lead to the phenotypic manifestations of genetic disorders may lead to the discovery of new pharmacologic interventions. The ichthyoses are characterized by scaling, inflammation, and an impaired epidermal barrier. Recent studies have uncovered T helper type 17 skewing in ichthyotic skin, resembling psoriasis, and high frequencies of IL-17− and IL-22−expressing T cells in blood, correlating with severity and transepidermal water loss. Repurposing systemic T helper type 17/IL-23−inhibitory therapies for psoriasis may prove useful for patients with ichthyosis.

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Our understanding of the mutations underlying genetic disorders, including those with prominent skin manifestations, has tremendously increased during the past two decades because of the availability of new tools for discovery, in particular whole-exome and whole-genome sequencing. Linking a skin disease with a specific gene, especially a gene with a product not previously explored in skin, opens the door for studies that explore the localization and function of gene expression products in skin and how they are altered by disease. Similarly, finding that a disease phenotype can be replicated by mutations in several genes suggests that their gene products interact or share a pathway in tissue that leads to a similar clinical effect.

Discoveries of underlying gene mutations have also led to great excitement about the potential to leverage this knowledge toward therapeutic benefit. New technologies to introduce a normal gene or functioning gene product are considered the ideal therapy, with gene therapy optimal for "cure" of genetic disease, including genetic disorders with skin manifestations. For dominant negative disorders, gene knockdown approaches have been shown to reverse disease manifestations, such as in the pilot human study with injected small interfering RNA targeting abnormal *KRT6A*, encoding keratin 6A, in a patient with pachyonychia congenita (Leachman et al., 2010). Approaches for topical delivery enabling knockdown of gene expression are also in development for genetic (Kaspar et al., 2016) and inflammatory (Lewandowski et al., 2017; Randeria et al., 2015) skin disorders. For disorders in which the mutation reduces gene and protein expression, progress has been made through introducing the normal gene and expanding corrected cells for skin transplantation for life-threatening junctional (Hirsch et al., 2017; Mavilio et al., 2006) and dystrophic forms (Siprashvili et al., 2016) of epidermolysis bullosa. Furthermore, the ability to introduce corrected genes into stem cells promises to both improve transplantation of corrected cells and potentially direct introduction systemically to reach target sites (Vanden Oever et al., 2018). Newer technology using gene editing has yet to reach human trials for skin disease, but it is showing great potential in vitro and in early animal models.

CAN TARGETED PHARMACOLOGIC THERAPY FOR PSORIASIS AND ATOPIC DERMATITIS BE REPURPOSED FOR INFLAMMATORY DISEASES WITH A MONOGENIC BASIS?

Although these curative gene-based therapies are in development, there remains a significant need for new approaches to treating genetic skin disorders. Pharmacologic approaches require an improved understanding of the changes in mRNA and protein expression that result from gene alteration. Fortunately, technological developments have also allowed scientists to uncover alterations in expression patterns in disease using relatively small skin biopsy samples or blood samples and to correlate these alterations in expression with phenotypic manifestations of skin disease. These technologies have been applied to understand immune system skewing in inflammatory skin disorders, such as psoriasis (Kim and Krueger, 2017) and atopic dermatitis (AD) (Brunner et al., 2017) and have contributed greatly to the ongoing emergence of new targeted therapeutic options for treating these inflammatory skin disorders. In the case of psoriasis, these studies led to the availability of highly successful biologics that inhibit tumor necrosis factor-α (TNF-α). More recent discoveries showing the importance of activation of T-helper (Th) type 17/IL)-23 signaling pathways (with TNF-α activation as a synergistic pathway) have led to the commercial availability of even more effective systemically administered monoclonal antibodies that target IL-23, IL-17A, or IL17RA (the IL-17A/F receptor). In AD, mRNA expression studies in both adult and early pediatric skin have shown that Th2/Th22 pathways are activated (Esaki et al., 2016; Mansouri and Guttman-Yassky, 2015), and clinical trials have led to the

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Abbreviations: AD, atopic dermatitis; ARCI, autosomal recessive congenital ichthyosis; CIE, congenital ichthyosiform erythroderma; EI, epidermolytic ichthyosis; LI, lamellar ichthyosis; NS, Netherton syndrome; RT-PCR, reverse transcriptase-PCR; TEWL, transepidermal water loss; Th, T helper; TNF, tumor necrosis factor

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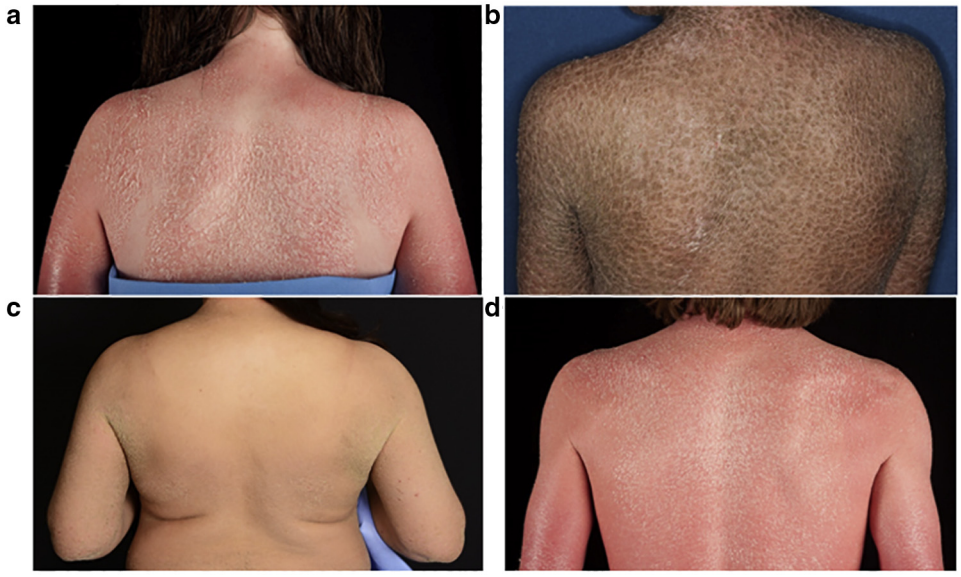

Figure 1. Major orphan forms of ichthyosis. Representative images showing the scaling and variable erythema of (**a**) congenital ichthyosiform erythroderma, (**b**) lamellar ichthyosis, (**c**) epidermolyic ichthyosis, and (**d**) Netherton syndrome.

recent commercial availability of the first Th2-targeting monoclonal antibody (Simpson et al., 2016).

Inflammation is a common phenotypic manifestations of several inherited disorders of skin, raising the possibility that commercially available and pipeline therapeutics that target common inflammatory diseases could be harnessed toward genetic skin disorders. The possibility of "repurposing" drugs that are existent or already in clinical trials allows for the very rapid transition from laboratory-based discovery to clinical trials and use by patients, in contrast to the long delay from discovery to commercial availability if trials show achievement of primary endpoint(s). An additional benefit of treatment based on discovery of the molecular expression patterns, downstream of genetic alteration, is the ability to find shared molecular disease characteristics that correlate with phenotypic manifestations, enabling treatment of groups of patients who share molecular characteristics, rather than the potentially more restrictive personalization at the gene mutation level.

THE ICHTHYOSES: A GROUP OF RARE DISORDERS WITHOUT SATISFACTORY THERAPY

Ichthyosis is a group of genetic disorders resulting from variants in more than 50 genes. The clinical feature that characterizes ichthyosis, regardless of underlying genetic basis, are scaling, usually generalized and in association with inflammation (Mazereeuw-Hautier et al., 2018; Takeichi and Akiyama, 2016; Vahlquist et al., 2018). However, all forms of ichthyosis have been associated with protein and lipid abnormalities that lead to a defective epidermal barrier, manifesting functionally as increased transepidermal water loss (TEWL). Ichthyosis vulgaris typically results from heterozygous or compound heterozygous mutations in *FLG*, the gene encoding the barrier protein filaggrin, and is a common disorder (approximately 10% of individuals) that is associated with an increased risk of developing AD (Baurecht et al., 2007). Although less common (up to 1:1,500 males), recessive X-linked ichthyosis results from mutations in *STS*, encoding steroid sulfatase, in which accumulation of cholesterol sulfate promotes corneocyte retention (Elias et al., 2004). Ichthyosis vulgaris and recessive X-linked ichthyosis usually respond well to topically applied emollients and keratolytic agents.

In contrast, there are dozens of rarer ("orphan") forms of syndromic and nonsyndromic ichthyosis (Oji et al., 2010). The most common among these orphan forms of ichthyosis are autosomal recessive congenital ichthyosis (ARCI), with its phenotypic spectrum from congenital ichthosiform erythroderma (CIE) to lamellar ichthyosis (LI), Netherton syndrome (NS) (also autosomal recessive), and epidermolytic ichthyosis (EI) (autosomal dominant) (Vahlquist et al., 2018) (Figure 1). Biallelic mutations in *TGM1*, encoding transglutaminase 1, cause most cases of LI, whereas mutations in 10 other genes, many of which are involved in the lipoxygenase pathway or lipid metabolism (*ABCA12*, *ALOX12B*, *ALOXE3*, *CERS3*, *CYP4F22*, *LIPN*, *NIPAL4*, *PNPLA1*, *SDR9C7*, and *SLC27A4/FATP4*), more commonly lead to the CIE or an intermediate phenotype of variable severity (Richard, 2018; Shigehara et al., 2016; Vahlquist et al., 2018). NS results from mutations in *SPINK5*, leading to deficiency of the proteinase inhibitor LEKTI (lympho-epithelial Kazal-type-related inhibitor), whereas EI most commonly occurs from heterozygous mutations in *KRT10* or *KRT1*. In general, these orphan forms cause a much greater burden, including on quality of life, and are a greater treatment challenge. Available treatments, primarily systemic or topical retinoids, promote keratinocyte differentiation and shedding, thereby reducing scaling and skin thickening. Retinoids sometimes improve, but more often increase, skin inflammation.

Although the inflammation, cutaneous thickening, and scaling that characterize the ichthyoses are traditionally attributed to the cardinal barrier defect, few studies have addressed the molecular basis for these phenotypic features. However, understanding the pathway to phenotypic features could lead to more effective, targeted therapeutic approaches. For example, absence in CHILD syndrome (i.e., congenital hemidysplasia, ichthyosiform erythroderma, and limb defects) of the *NSDHL* gene, encoding nicotinamide adenine dinucleotide phosphate–dependent steroid dehydrogenase-like, was recognized to lead to both

cutaneous deficiency of cholesterol and accumulation of toxic early pathway components toward cholesterol biosynthesis. By both blocking the pathway upstream of NSHDL and correcting the deficiency of the cholesterol end product with a topically applied compounded medication containing lovastatin and cholesterol, clinical, histological, and ultrastructural cutaneous changes of CHILD syndrome were markedly improved within 6 weeks (Paller et al., 2011).

FEW INVESTIGATIONS OF BIOMARKERS IN HUMAN AND MOUSE MODEL ICHTHYOTIC SKIN AND BLOOD

Most investigations with human ichthyotic skin have focused on barrier alterations, such as epidermal hyperplasia/increases in *KRT16* and *KRT6B*, and abnormalities in differentiation (*LOR*, *FLG*) and lipid metabolism genes (Descargues et al., 2006; Pavez Lorie et al., 2009). Few have studied the potential role of inflammatory dysregulation in disease development, and most of these have focused on NS; more comprehensive analysis of skin from patients with ichthyosis has only recently been performed. Nevertheless, these early studies suggest an interplay among expression of proinflammatory cytokines and chemokines, epidermal hyperkeratosis, and barrier abnormalities. For example, human NS keratinocytes, human keratinocytes incubated with kallikrein 5, and skin from *Spink5*$^{-/-}$ mice have shown increases in *PAR2*, *TSLP*, *IL1b*, *IL8*, and *TNF* mRNA expression (Briot et al., 2009); however, inactivation of PAR2 (protease-activated receptor 2) did not reduce the cutaneous inflammation in an adult NS mouse model, despite inhibiting *TSLP* expression (Briot et al., 2010). In another study, NS mouse models showed diverse cytokine activation with increases in mRNA levels of genes encoding innate, Th2, Th17, and Th22 cytokines (IL-1β, TNF-α, IL-4, IL-13, IL-17, and IL-22) and corresponding chemokines (TSLP, CCL17, CXCL1, CCL20, and S100A8/9) (Furio et al., 2014), and increases in IL-33 were uncovered in the skin of two patients with NS (Konishi et al., 2014). In LI organotypic cultures, IL-1α receptor antagonists block hyperkeratosis (O'Shaughnessy et al., 2010), whereas IL-37β partially suppressed the cutaneous phenotype in *Abca12*$^{-/-}$ mouse models of harlequin ichthyosis through reduction of increased chemokine expression (Cottle et al., 2015). In addition, *Krt1*-knockout mice (EI) have increased IL-18, and depleting IL-18 partially rescues the EI skin phenotype (Roth et al., 2012). In the few studies of blood from patients with NS, levels of selected polar cytokines were increased (Akagi et al., 2013; Hosomi et al., 2008; Renner et al., 2009; Van Gysel et al., 2001), but there was inconsistent evidence of Th2 skewing.

Therapeutic interventional studies, coupled with investigation of cytokine alterations, have provided further evidence of cytokine alteration with improvement, although expression of only selected cytokines has been evaluated. In a patient with NS, Fontao et al. (2011) found an increase in mRNA expression of several cytokines in lesional skin (IFN-γ, IL-6, IL-8, IL-10, IL-17, and IL-23, but not IL-4, IL-5, or IL-31) and nonlesional skin (TSLP, TNF-α, and TGF-β). Infliximab therapy led to clearance of inflammation (but not xerosis, scaling, and serum IgE levels) by 1 year with reduction in all cytokines in lesional skin, except in *IL10* and *TNFA*, both of which remained increased. In another NS patient, 4 months of omalizumab therapy (with pulsed steroids in the first month) led to marked clinical improvement in association, with more than 50% reduction in blood levels of IL-1β, IL-5, and IL-17 (TNF was not assessed) (Yalcin, 2016). Although retinoids are not thought to primarily reduce skin inflammation, reduced *TNFA* expression was noted in a patient with LI treated with oral liazarole, which increases endogenous retinoid levels (Pavez Lorie et al., 2009).

DEMONSTRATION OF TH17 SKEWING IN ICHTHYOTIC SKIN AND BLOOD

The first more comprehensive assessment of mRNA expression of proinflammatory cytokines and chemokines as a function of ichthyosis disease severity was recently published (Paller et al., 2017). mRNA expression patterns for 54 genes that encode proteins involved in skin barrier formation and T-cell differentiation were assessed by reverse transcriptase-PCR from the lesional skin of 21 patients, 10 years of age and older, with the most common subtypes of orphan ichthyosis (ARCI-LI, ARCI-CIE, EI, and NS) of variable severity. Data were compared with mRNA in skin from age-matched healthy control individuals and adult patients with AD or psoriasis. TEWL measurements from the upper arm were all high, with the NS and CIE subtypes significantly higher than LI and EI subtypes. Compared with age-matched controls, all subtypes of ichthyosis had strong Th17 skewing (e.g., significant increases in mRNA econding IL-17A, peptidase inhibitor 3/PI3, CCL20, DEFB4B, and the S100As). IL-23p19 was increased only for CIE and NS, IL-12/IL-23p40 only for CIE, and IL-22 for both CIE and NS. Some Th1 markers were increased in some patients, without correlation with disease severity; markers of general inflammation, innate immunity, and Th2 markers were minimally or not increased (for representative examples, see Figure 2). The Th17 skewing for several markers was comparable or greater to that seen in the skin of adults with psoriasis. IL-17A expression correlated well with the disease severity ($r = 0.57$) and even more strongly with the erythema subscore severity ($r = 0.74$).

Subsequent analysis by gene array of skin from 29 patients with these forms of ichthyosis, including 21 from the RT-PCR study, showed 132 differentially expressed genes that were shared among the ichthyoses compared with age-matched healthy control skin (Malik et al., 2019). In addition to those found to be up-regulated in the initial RT-PCR study, this microarray analysis showed additional *IL17* and *TNFA* co-regulated genes recognized to be markers of psoriasis (e.g., *IL17F*, *IL36B/G*, *IL36R*, *KYNU*, and *VNN3*). The increases in Th17 expression correlated with TEWL as well as severity. Although the ichthyoses lacked the reduction in expression of genes encoding proteins of differentiation and tight junctions (e.g., *LOR*, *FLG*, and *CLDN1*) seen in AD, several alterations in lipid metabolism genes were notable among the ichthyoses, including encoding an enzyme that promotes chain elongation in the synthesis of very-long-chain ceramides and fatty acids. These gene expression changes were accompanied by reduction and abnormal distribution of lipids in frozen biopsy sections. Although IL-17 has been shown to reduce lipid-related gene expression in preadipocytes (Lee et al., 2017; Zuniga et al., 2010), the potential

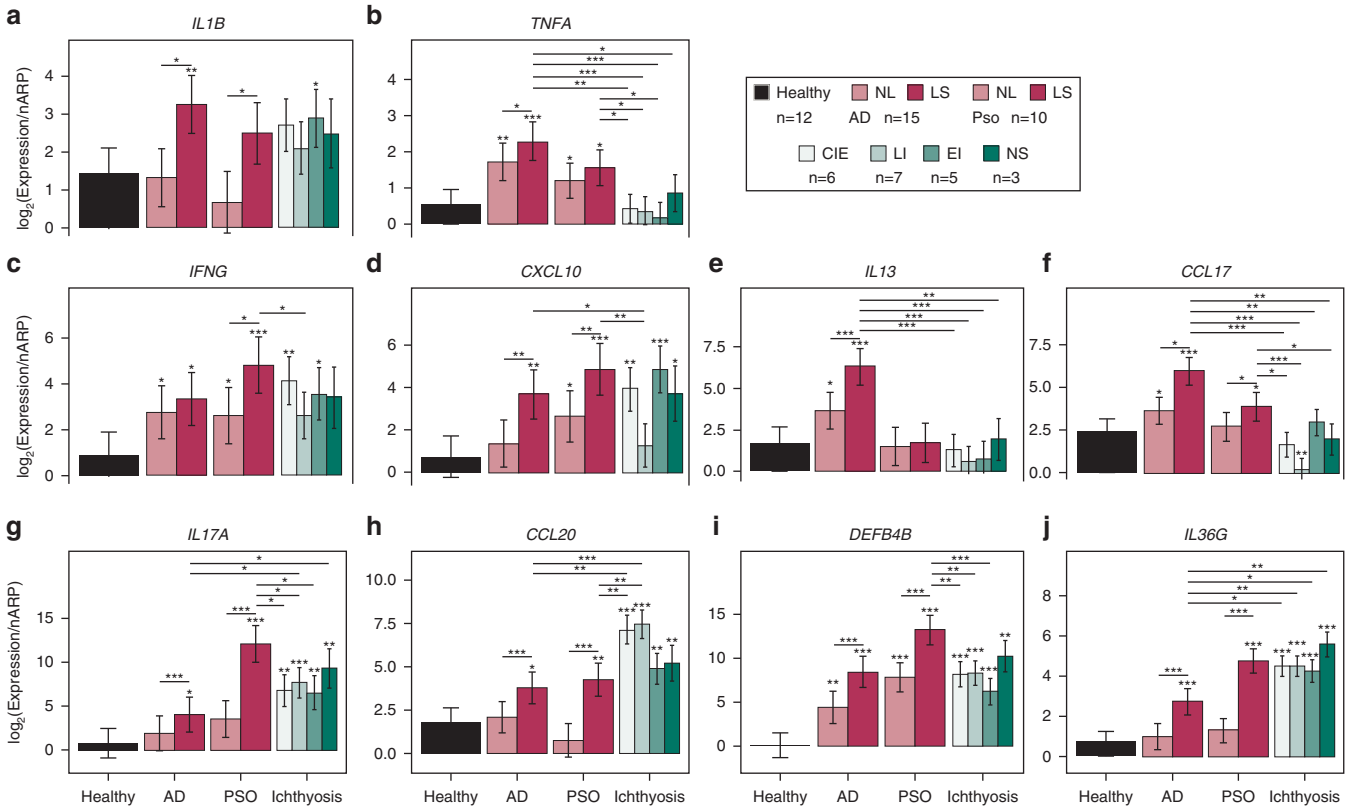

Figure 2. *IL17/TNFA* synergistic/additive gene expression is increased in ichthyosis. Expression of 42 immune genes was evaluated using reverse transcriptase-PCR from ichthyotic skin and compared with gene expression in control samples and the nonlesional (NL) and lesional skin (LS) from individuals with atopic dermatitis (AD) or psoriasis (Pso). mRNA $\log_2$ values were adjusted to hARP expression levels. Graphs shown represent (**a, b**) innate immunity, (**c, d**) Th1 cytokines, (**e, f**) Th2 cytokines, and (**g–j**) Th17/Th17-related cytokines. Asterisks directly over bars are *P*-values compared with control samples. Lines with associated asterisks define the comparators at either end of the lines. LS_{mean} ($\log_2$ expression/hARP) ± SEM. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. TEWL, transepidermal water loss; Th, T helper; TNF, tumor necrosis factor.

relationship between Th17 cytokines and epidermal lipid expression is poorly understood and deserves investigation.

Gene array analyses also showed some distinct expression patterns among the ichthyoses, which may contribute to their differences in clinical manifestations (Malik et al., 2019). For example, NS showed the greatest T-cell activation and a broader immune phenotype than other subtypes. EI, in contrast to the other three subtypes, did not show significant lipid abnormalities. Patients with LI had the most severe reduction in lipid metabolism genes and the most atypical Nile red lipid staining pattern, possibly because transglutaminase 1, which was deficient in LI patients, crosslinks the epidermal ω-hydroxyceramides to terminal differentiation proteins. Future studies with larger numbers of ichthyosis patients will be required to further delineate the differences among ichthyosis subtypes and even individuals with the same clinical phenotype and gene alteration.

Given the growing recognition that inflammatory skin disorders can be associated with systemic immune system activation, blood from patients with these orphan forms of ichthyosis was also analyzed. Serum samples from the ichthyoses had increased IL-17A protein expression, as shown by Erenna immunoassays (Malik et al., 2019). Furthermore, there was a high frequency of activated cutaneous lymphocyte antigen-positive and cutaneous lymphocyte antigen-negative T cells that expressed IL-17 ($P < 0.05$) and IL-22 ($P < 0.01$) from 47 patients with ichthyosis, particularly the NS and CIE subtypes, compared with with blood cells from healthy control individuals (Czarnowicki et al., 2018). These high frequencies clustered with severity and TEWL. The peripheral blood lymphocyte skewing toward Th17/IL-22 polarity raises the question of risk of systemic comorbidities, as occurs in psoriasis, particularly cardiovascular and joint inflammation, which have received little attention in ichthyosis beyond the association of arthritis as a comorbidity of harlequin ichthyosis, a severe subset of ARCI (Beazley et al., 2011; Chan et al., 2003; Clement et al., 2007; Rajpopat et al., 2011).

WHAT IS THE SIGNIFICANCE OF TH17 SKEWING IN ICHTHYOSIS?

The significance of Th17 skewing in ichthyosis and its specificity as a marker is unclear. It is possible that the shared Th17 activation is merely the response to the impaired barrier and a compensatory attempt to protect against organisms. Although innate immune response markers are known to be increased after barrier impairment by tape stripping (Dickel et al., 2010), no studies have looked at the Th17 pathway response. Similarly, few studies have broadly assessed the T-cell immune molecular phenotype for inflammatory disorders. AD, characterized by barrier impairment, features skewing toward Th2/Th22 immune responses, with Th17 response to a much lesser extent and only in select

populations (Asians, young children) (Esaki et al., 2016; Noda et al., 2015). The psoriasiform dermatitis induced by TNF inhibitors, particularly in patients with Crohn disease, has now been shown to have a biomarker pattern distinct from either AD or psoriasis, with a strong IFN-γ activation signature (Stoffel et al., 2018). Molecular immunophenotyping of skin samples has shown allergic contact dermatitis to be a heterogenous disorder in which some allergens trigger a Th1/Th17 response (e.g., nickel) and others a Th2 response (e.g., fragrance) (Dhingra et al., 2014). In a recent gene array analysis of chronic venous wound skin (vs. healthy skin), 2-fold increases were noted for almost 3,500 genes, among them some encoding innate immune responses (IL-6; IL-8; β-defensin 2; *S100As*) and a few IL-17 and TNF-α co-regulated genes (*IL36G*, *KYNU*), but not *CCL20*, *CXCL1*, or *IL17A* (Stone et al., 2017). In a form of epidermolysis bullosa simplex, a chronic blistering disorder with associated inflammation, five immune response genes were differentially up-regulated compared with normal skin, based on gene arrays; these included *CCL22* (Th1) and *CCL5/RANTES* (Th2), but none from the Th17 pathway (Bchetnia et al., 2013). Response to medication has recently been suggested as an additional marker for correlating suspected immune phenotype with clinical morphology (Eyerich and Eyerich, 2018). In addition to the Th2 and Th17/Th22 responses of AD and psoriasis, respectively, Th1 lymphocyte subsets were proposed to drive lichenoid responses (including in lupus erythematosus) (biomarkers such as IFN-γ and CXCL10) and regulatory T cells (biomarkers IL-10 and TGF-β) fibrogenic responses. Taken together, these data suggest that the strong Th17 skewing across the ichthyoses as a group is disease-specific and not a common phenotype for chronic inflammatory disease, even with barrier abnormalities.

The other consideration is that the Th17 skewing is a response to the barrier defects that leads to inflammation and scaling. Th17 and TNF co-regulated genes are thought to cause the inflammation and scaling of psoriasis, and administration of Th17-targeting medications dramatically improves disease severity. Recently, two patients with syndromic ichthyosis from mutations in *DSP*, encoding desmoplakin, experienced dramatic improvement in ichthyosis severity (both erythema and scaling) and TEWL from use of ustekinumab, which inhibits IL-12/23p40 (Paller et al., 2018). In one of those patients, immunophenotyping of skin and blood was performed. In skin, expression of IL-17A, but also IL-22/IL-23p40 and IL-22, was increased as shown by RT-PCR analysis, and the frequency of IL-17− and IL-22−producing T cells was shown to be elevated by single-cell flow cytometry, which led to the decision to treat with ustekinumab.

The shared Th17 signal among the orphan ichthyoses and the ameliorative result of Th17/IL-23 inhibition in a patient with a form of syndromic ichthyosis suggest that the Th17 skewing plays a pathogenic role in ichthyosis. To further test this possibility, a 16-week double-blind, randomized, placebo-controlled trial of the Th17 inhibitor secukinumab has been initiated (NCT03041038). This trial will help unravel the complex relationship between IL-17 and clinical features/barrier issues related to ichthyosis.

In conclusion, there is a significant unmet need for new treatments for patients with genetic skin disorders. Looking beyond the underlying genetic basis toward the molecular changes that may lead to phenotypic characteristics may provide insight, not only on understanding these genetic disorders but also on new therapeutic directions. The rapidly expanding repertoire of systemic therapies that target specific immune-polarized T-cell subsets provides the opportunity for repurposing commercially available medications toward a variety of inflammatory skin disorders, including monogenic disease.

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CONFLICT OF INTEREST
ASP is an investigator for Novartis Eli Lilly and Janssen, makers of anti-Th17/IL-23 monoclonal antibodies, and has been a consultant with honoraria for Novartis and Eli Lilly.

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