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Genetic Pathways in Disorders of Epidermal Differentiation

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Abstract

More than 100 human genetic skin diseases, impacting over 20% of the population, are characterized by disrupted epidermal differentiation. A significant proportion of the 90 genes identified in these disorders to date are concentrated within several functional pathways, suggesting the emergence of organizing themes in epidermal differentiation. Among these are the Notch, TGF β , IKK, Ras/MAPK, Phosphoinositide 3-kinase, p63, and Wnt signaling pathways as well as core biologic processes mediating calcium homeostasis, tissue integrity, cornification, and lipid biogenesis. Here, we review recent results supporting the central role of these pathways in epidermal differentiation, highlighting the integration of genetic information with functional studies to illuminate the biological actions of these pathways in humans as well as guide development of future therapeutics to correct their dysfunction.

Keywords

epidermis; differentiation; genetics; skin disease; keratinocyte

Epidermal diseases arise from aberrant epidermal differentiation

The epidermis is a self-renewing stratified epithelial tissue that forms the outer barrier of the skin. As such, its function is to protect the organism from outside insults, such as bacterial pathogens, and to prevent water-loss. The epidermis encompasses distinct layers of keratinocytes: the basal layer consists of self-renewing progenitor cells; the spinous layer, lying above the basal layer, consists of upward migrating, differentiating keratinocytes; the granular layer, consists of cells producing the substrates necessary to form the impermeable barrier; and the stratum corneum consists of terminally differentiated enucleated lipid-rich corneocytes that have undergone cornification to form the outer skin surface (Figure 1). Epidermal self-renewal and the mechanisms of stem cell maintenance have been recently reviewed [1]. Here, we focus on genetic alterations underlying epidermal disorders caused by dysfunction of epidermal differentiation, organized by the biological process or signaling pathway most affected (Table 1).

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Loss of tissue integrity

Epidermal differentiation is dependent on proper structural architecture, and this begins with the structural integrity of the keratinocyte, which is critical for forming a squamous epithelium. Keratin intermediate filaments (**KIF**) form a network essential for cellular organization and cytoskeletal structural integrity to withstand mechanical stress. Keratins 5 and 14 are expressed in the basal layer of the skin and are replaced by keratins 1 and 10 in the differentiated suprabasal layers. Mutations in *KRT5* and *KRT14* are associated with a subset of **epidermolysis bullosa (EB)**, a heterogeneous skin disease characterized by detachment of the epidermis from the dermis and severe blistering (Figure 2) [2,3]. In epidermolysis bullosa simplex (EBS), the severity of disease frequently correlates with the site of mutation in *KRT5* and *KRT14*, with mutations in the region responsible for linking the small acidic type I keratins (*KRT1*, *KRT5*) to the larger neutral-basic type II keratins (*KRT10*, *KRT14*) giving rise to more severe phenotypes due to the overall disturbance of the KIF network [2]. A recent study investigating the genomic changes occurring in EB versus normal skin confirmed recurrent mutations in *KRT5/KRT14* and identified EB gene signatures that point to dysfunction in lipid metabolism as well as epidermal keratinization [4]. EB is also characterized by mutations in various cell adhesion genes, including lamin 332, integrins, and collagen VII recently reviewed in [5]. Among the mutations in EB associated with hemidesmosome, a recent knock-in mouse model of **Epidermolysis Bullosa Simplex-Ogna** exploits a mutation in the hemidesmosome component, plectin 1a. The EBS-Ogna mutation leads to degradation of plectin 1a and results in disorganization of hemidesmosome assembly leading to skin blistering in response to trauma [6]. Together, these findings provide insight into novel molecular mechanisms of EBS and present a model to test potential therapeutic treatments for this specific type of EB.

Mutations in *KRT1* and *KRT10* are characteristic of **epidermolytic hyperkeratosis**, a skin disease initially characterized by redness and blistering later developing hyperkeratosis (Figure 2) [2,7]. While deletion of *KRT10* in humans results in a severe skin phenotype, *KRT1^{-/-}/KRT10^{-/-}* mice do not display blistering or hyperkeratosis observed in humans, perhaps due to the abundance of hair follicles on the skin of mice [2,8]. Of note, the mouse model suggests the involvement of desmosomes, components of the cell adhesion machinery, showing that Krt1 and Krt10 are necessary for proper desmosome formation and overall cytoskeletal structure [8]. Interestingly, dominant mutations in *KRT10* have recently been identified in **ichthyosis with confetti**, a rare disease characterized by skin redness, blistering, and skin thickening [9]. The authors observed that, through mitotic recombination, certain areas of the skin reverted back to wild-type *KRT10* status. This rare event may be therapeutically targeted to correct the *KRT10* mutation in this disease and possibly be employed in other diseases with dominant keratin mutations harboring a wild-type allele.

Disruptions in calcium-signaling

Calcium signaling is recognized for its exquisite control of terminal differentiation in keratinocytes. Hallmarks of epidermal differentiation are dependent on different stages in the calcium-signaling cascade; an intracellular calcium gradient increases from the basal layer to

the stratum corneum. Calcium signaling in keratinocytes begins with binding of Ca^{2+} to plasma membrane Ca^{2+} receptor (CaR) which stimulates differentiation by inducing E-cadherin-mediated cell-cell adhesion and transcription of differentiation-specific genes [10,11]. Release of intracellular Ca^{2+} stores stimulates influx of extracellular Ca^{2+} through transient receptor protein channels (TRPC). Calcium pumps, sarco/endoplasmic reticulum Ca^{2+} ATPase isoform 2 (SERCA2) and secretory pathway $\text{Ca}^{2+}/\text{Mn}^{2+}$ ATPase isoform 1 (SPCA1), replenish intracellular Ca^{2+} stores in the endoplasmic reticulum (ER) and Golgi, respectively. Depletion of ER Ca^{2+} induces XBP1-mediated ER stress signaling, which enhances epidermal differentiation, similar to physiological processes that occur during normal barrier wound repair [12].

Calcium homeostasis is pathologically perturbed in **Darier Disease (DD)** and **Hailey-Hailey Disease (HHD)**, which are characterized by autosomal-dominant mutations in the calcium ATPases *ATP2A2* encoding SERCA2 and *ATP2C1* encoding SPCA1, respectively [13,14]. Keratinocytes isolated from DD and HHD lesions contained less calcium in the basal layer compared with normal keratinocytes, as well as abnormal expression of keratins 10 and 14 and the ATP receptor P2X7, suggesting an overall defect in keratinocyte differentiation [15]. Compensatory mechanisms to restore intracellular Ca^{2+} exist in DD keratinocytes, including up-regulation of SPCA1 and the TRPC1 Ca^{2+} channel [16,17]. Furthermore, differentiation defects caused by SERCA2 inhibition in keratinocytes can be rescued by inhibiting the breakdown of sphingosine-1-phosphate (S1P), thereby representing a novel approach to treat DD [18]. Intracellular SIP has also been demonstrated to enhance expression of Ca^{2+} dependent differentiation genes [19].

Desmosomal dysfunction in the epidermis

Intercellular junctions in the epidermis are formed by tight junctions, hemidesmosomes, desmosomes and corneodesmosomes, attach to intermediate filaments within the cell, and impart the ability to withstand mechanical stress [20,21]. Three families of proteins make up the desmosome: desmosomal cadherins (desmocollins/desmogleins), plakins, and armadillo proteins (plakoglobin). Mutations in various desmosomal components (*DSG1*, *DSC3*, *JUP*, *PKP1*, *DSP*, *CDSN*) are observed in **Palmoplantar Keratoderma (PPK)** and **Striate PPK** [21]. Desmoglein 1 (Dsg1) expression is limited to the suprabasal layer, particularly at the interface of the basal and suprabasal layer, suggesting an important role for Dsg1 in structural morphology linked to terminal differentiation. Mutations in *DSG1* are characterized by increased intercellular spaces in the skin and partial detachment of keratinocytes from the suprabasal layer [22]. Depletion of *DSG1* in an organotypic model of human epidermis also leads to this phenotype along with concurrent loss of *DSC1* expression, which encodes a companion cadherin to Dsg1 [21]. Intriguingly, epidermal differentiation defects due to *DSG1* depletion can be rescued in a desmosome-independent manner. Increased EGFR-ERK1/2 signaling resulting from *DSG1* depletion was reduced after introduction of a Dsg1 mutant unable to bind desmosomal components, suggesting that Dsg1 itself promotes differentiation by regulating growth signaling [21].

Mutations in the gene *JUP*, which encodes plakoglobin (PG), a Dsg1 binding partner, have been linked to skin fragility, including a nonsense mutation in EB [21]. Similar to what is

observed in humans, a recent study showed that *JUP*^{-/-} mice have altered epidermal differentiation marked by epidermal hyperproliferation, atypical desmosomes, and increased intercellular spaces [23]. Mutation of desmoplakin (DP), a linker between desmosomes and the KIF network, also results in PPK. Interestingly, DP has been linked to microtubule organization based on the finding that centrosomal proteins Lis1 and Ndel1 re-localize to the cell cortex upon calcium-induced differentiation in a DP-dependent manner [24]. The conclusions drawn from these studies suggest exquisite crosstalk between cell adhesion and epidermal differentiation, much of which remains to be carefully elucidated.

Mutations in additional cell adhesion molecules include a mutation in *PVRL4*, which encodes nectin-4, a protein involved in forming adherence junctions, identified in patients suffering from ectodermal dysplasia. The mutation prevented its association with nectin-1, and analysis of diseased skin displayed mislocalization of desmosomal components [25]. Furthermore, mutations in *CSTA*, a protease inhibitor of cystatin A, have recently been described in **exfoliative ichthyosis**. By means of a mechanical stretch assay and an organotypic model of epidermis in which *CSTA* was depleted, overall epidermal disorganization distinguished by hyperkeratosis, disturbance of the basal epidermal architecture, and expanded intercellular spaces was observed [26]. Although these findings suggest a role for cystatin A in cell-cell adhesion, no defect in barrier formation was detected.

A nonsense mutation in *CDSN*, encoding corneodesmosin, a glycoprotein localized to the extracellular part of the corneodesmosome joining the desmosome core to the cornified envelope, has been attributed to generalized peeling skin disease. Affected skin cells deficient in *CDSN* were reconstituted in an organotypic model and revealed a less organized epidermis with irregular expression of late differentiation markers and severe epidermal barrier defects [21]. Likewise, *CDSN*^{-/-} mice display detachment of the stratum corneum at sites of friction and trauma and die shortly after birth due to these skin defects [21]. Furthermore, skin grafts of these mice exhibit hair defects and psoriasis-like lesions.

Mutations in cornification and lipid metabolism

In the stratum corneum, keratinocytes undergo terminal differentiation into corneocytes, enucleated cells surrounded by a lipid-rich cornified envelope. The organization of the stratum corneum has been compared to a brick wall, where the corneocytes represent the “bricks” surrounded by extracellular matrix of non-polar lipids, the “mortar” [27]. Granular cells just below the stratum corneum secrete lamellar bodies (LB), which consist of a distinct composition of phospholipids, cholesterol sulfate, glucosylceramides, and catabolic enzymes, into the intercellular spaces. Here, the lipids are enzymatically converted into free fatty acids, cholesterol, and ceramides and then assembled into lamellar membranes in the stratum corneum interstices. Together, the skin forms a robust permeability barrier that prevents trans-epidermal water loss. The formation and maintenance of the permeability barrier is in part dependent on the KLF4 and GRHL3 transcription factors, as well as Wnt-mediated T cell factor (TCF)/lymphoid enhancing-binding factor 1 (Lef1) signaling [28–30].

Impaired permeability barriers are observed in a heterogeneous family of monogenic disorders with underlying ichthyosis. Among common mutations in genes important in epidermal differentiation are those in the *FLG* gene. *FLG* encodes the profilaggrin protein, which is critical for formation of keratohyaline granules and whose absence causes ichthyosis vulgaris and contributes strongly to the pathogenesis of atopic dermatitis (Figure 2) [31]. Of note, *FLG* expression is altered in psoriasis and GWAS studies have identified mutations in late-cornified envelope genes *LCE3B* and *LCE3C* [32].

Defects in lipid metabolism or transportation can alter the lamellar membrane leading to barrier abnormalities. Such defects underlie **lamellar ichthyosis (LI)** (Figure 2), a group of autosomal recessive ichthyoses without systemic involvement, as well as recessive X-linked ichthyosis (**RXLI**). Lamellar ichthyosis can arise from several genetic aberrations, including mutations in ATP binding cassette 12, (*ABCA12*), arachidonate lipoxygenase 12B and E3 (*ALOX12B*, *ALOXE3*), transglutaminase 1 (*TGMI*), patatin-like phospholipase 1 (*PNPLA1*), ichthyin (*ichthyin*), and cytochrome P450 4F22 (*CYP4F22*) [33]. While the mechanisms are not well understood, all mutations except *TGMI* affect the peroxidized lipid pathway, resulting in metabolite deficiency and substrate accumulation. By contrast, RXLI is caused by mutations in steroid sulfatase (SSase), which hydrolyzes cholesterol sulfate (CSO₄) to cholesterol, and is characterized by defects in permeability barrier and desquamation. Excess CSO₄ results in lamellar membrane phase separation and inhibition of corneodesmosome proteases, kallikrein 5 and 7 (KLK5 and KLK7), disrupting the permeability barrier and inhibiting desquamation [34].

Mutations in *ABCA12* prevent proper delivery of glucosylceramides from the Golgi apparatus into LB. Missense mutation in one allele of *ABCA12* is clinically distinct from truncation or deletion mutations in both alleles, resulting in the milder type II LI and the more severe **Harlequin's ichthyosis (HI)**, respectively [35]. Corrective gene transfer of *ABCA12* in HI keratinocytes rescued ABCA12 expression and LB formation/secretion, suggesting *ABCA12* mutations disrupt LB lipid assembly [35]. Moreover, in HI patients with residual ABCA12, topical treatments with activators of peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR) as well as ceramides, glucosylceramide precursors, have been successful in rescuing ABCA12 expression [36,37]. Loss of *ABCA12* also leads to abnormal desquamation caused by decrease in expression of KLK5 and cathepsin D proteases, suggesting that ABCA12 regulates both permeability barrier homeostasis and desquamation [35].

Pathways of epidermal homeostasis and dysfunction

Epidermal homeostasis requires a finely tuned balance between basal layer proliferation and commitment to terminal differentiation. Multiple pathways regulate epidermal progenitor exit from the cell cycle and transition into the process of barrier formation, including the TGFβ/SMAD, NF-κB, PI-3K/PTEN, and NOTCH signal transduction pathways [38–42]. At the center of all these processes exists the p53 family member, *TP63*, essential for both the proliferative capacity and differentiation potential of epidermal progenitors [43,44].

TP63-ZNF750-KLF4 transcriptional circuit in epidermal disorders

TP63 exists in multiple isoforms, but *Np63α* is the dominant isoform in developmentally mature epidermis. Heterozygous *TP63* mutations in the human syndromes **Ankyloblepharon-Ectodermal Dysplasia-Clefting (AEC)**, **Ectrodactyl-Ecotdermal Dysplasia (EEC)**, **Limb-Mammary syndrome (LMS)**, **Acro-Dermato-Ungual-Lacrima-Tooth syndrome (ADULT)**, **Rapp-Hodgkin syndrome (RHS)**, and **Split-Hand/Foot Malformation (SHFM)** have been well chronicled [45]. Remarkably, mutations in the C-terminal sterile-alpha-motif (SAM) domain, specific to the *Np63α* isoform, give rise to AEC, the only *TP63* syndrome that presents with severe epidermal erosions. Interestingly, in addition to impaired expression of differentiation markers, including those involved in cell adhesion and barrier formation, AEC patient skin also presents with abnormal suprabasal Ki-67 staining, indicating dysregulated cell cycle exit may contribute to disease features [46]. A recent mouse model of AEC suggests this dysregulation is in part mediated by impaired FGF signaling [47].

Two recent studies have shed light on the pathomechanism of AEC mutant p63. Here, *ZNF750*, which is associated with familial psoriasis in two extended families, was found to be a direct target of *Np63α* and is required for the terminal differentiation of human keratinocytes [48–50]. Mechanistic analyses revealed that *ZNF750* is required for the induction of *KLF4*, which is essential for the barrier function of skin [30]. Follow up work further demonstrated that AEC mutant p63 prevented the transcriptional induction of *ZNF750* in an organotypic human tissue model [51]. Remarkably, forced expression of *ZNF750* rescued impaired epidermal differentiation resulting from AEC mutant p63. Together, these findings provide new insight into the existence of a p63-ZNF750-KLF4 network in human epidermal development and homeostasis.

TGFβ and IKK signaling in inherited epidermal neoplasia

TGFβ signaling participates in a multitude of biological processes including tissue homeostasis and carcinogenesis [52,53]. Although evidence supports a tumor promoting role for TGFβ signaling late in tumorigenesis, the downstream mediators of TGFβ, namely Smads -2, -3 and -4 have anti-proliferative activities in epithelial cells [54,55]. Suppression of Smad2 and Smad4 has been observed in human squamous cell carcinomas (SCCs) (Figure 2) supporting the finding of hyperplasia and spontaneous SCC in mice with conditional ablation of Smad4 in epidermis [39,54] **Multiple self-healing squamous epithelioma** (MSSE) is an autosomal dominant skin disorder characterized by rapidly growing SCC-like locally invasive tumors. Remarkably, after several weeks of growth, tumors spontaneously regress resulting in deep scars. Though the disease locus was mapped to 9q22.3 almost two decades ago, the lack of recombination events near this genomic region prevented identification of the disease gene. Using the powerful technique of exon capture and deep sequencing, a recent report identified loss-of-function mutations in *TGFBR1* in individuals with MSSE [56]. The IκB kinase α (IKK1) is critical for cytoplasmic initiation of non-canonical NF-κB signaling [57]. Independent of its kinase activity, and in a nuclear-dependent manner, IKK1 is also essential for epidermal progenitor cell cycle exit and terminal differentiation [58]. Consistent with these mouse studies, several

recent reports have demonstrated IKK1 re-localization, suppression, or deletion in SCC [59–61]. Interestingly, IKK1 physically interacts with Smad-2 and -3 and is required for nuclear accumulation of active Smad-2 and -3 in epidermis [55]. Taken together, these data support a critical role for a TGF β -Smad2/3-IKK1 axis in promoting epidermal differentiation and suppressing tumorigenesis. Of interest, IKK γ , encoded by *NEMO*, is mutated in **incontinentia pigmenti**, a disorder which manifests as epidermal hyperplasia, vesiculation, and resultant pigmentary abnormalities, as well as **hypohidrotic ectodermal dysplasia with immune deficiency** [62,63]. Unlike IKK1, which displays NF- κ B independent actions in epidermal differentiation, NEMO impacts appear largely mediated through IKK2 and the NF- κ B pathway, although the precise basis for its phenotypic impacts remain undefined. NEMO interacts physically with the *CYLD* gene product, a deubiquitinating enzyme that also binds the TRAF2 NF- κ B pathway regulator and, when mutated, can cause the benign neoplastic disorder of cutaneous epithelial neoplasms, **hereditary cylindromatosis** [64].

Cadherin and Wnt signaling defects

In addition to the desmosomal cadherins discussed above, classic cadherins regulate the actin cytoskeleton and also play a role in skin differentiation. Mice with deletion of both E-cadherin and P-cadherin display epidermal barrier defects and hyperthickening of the epidermis with a squamous appearance [65]. Although desmosomal function appeared to be unaltered, a defect in cell structure due to mislocalization of polarity proteins resulted in abnormal differentiation.

Wnts are small, secreted, lipid-modified morphogens involved in developmental signaling and differentiation. Mutations in *WNT10A* are associated with ectodermal dysplasia [66,67]. Wnts bind to extracellular receptors, effecting an intracellular signaling response, through β -catenin, converging on TCF/LEF transcription factors that act on Wnt target genes. Wnt signaling has been shown to play an important role in hair follicle self-renewal, although recent evidence points to a role for Tcf3 and Tcf4 in maintenance of the progenitor compartment of interfollicular epidermis. Peroxisome proliferator-activated receptor (PPAR) was shown to be a downstream target repressed by overexpression of Tcf3, thus promoting self-renewal by preventing lipid-mediated differentiation [68]. Whereas deletion of Tcf3 has no overt skin phenotype, deletion of both Tcf3 and Tcf4 results in hair follicle deficiency with thin skin due to diminished stem cell potential of interfollicular progenitor cells [69]. These findings appear to be independent of β -catenin-mediated signaling as the *Cnnb1*^{-/-} mouse displayed hyperproliferative skin rather than tissue collapse [69]. The cytoplasmic tails of classic cadherins bind β -catenin, which can in turn bind to α -catenin to regulate actin-cytoskeletal architecture and mediate cell signaling [70]. Moreover, mutational stabilization of β -catenin is responsible for the common skin neoplasm, pilomatricoma, and increased β -catenin signaling has been linked to cutaneous cancer stem cell maintenance [71,72]. A recent study also described an essential role for β -catenin in mediating proliferation in response to activation of ROCK, a Rho-GTPase responsible for actomyosin contractility [73]. In this study, β -catenin signaling in response to tissue stiffness resulted in a tumor-promoting environment. Together, these finds point to a crucial role for the integrity of cytoskeletal architecture in preventing tumorigenesis.

Notch in epidermal differentiation and tumor suppression

The role of Notch signaling in epidermal differentiation has been well studied. Notch is a transmembrane receptor whose activity is stimulated by extracellular ligand binding resulting in cleavage of its cytoplasmic domain, which functions as a transcriptional co-regulator serving to activate or repress target genes [74]. Notch protein expression is primarily localized to the suprabasal epidermis and has been shown to act in concert with AP-2 factors to regulate terminal differentiation [75]. Importantly, Notch has been implicated in skin tumorigenesis: loss of Notch1 in mice results in skin carcinoma formation as a result of a defective epidermal barrier and crosstalk with the underlying stroma, suggesting loss of Notch1 promotes tumorigenesis [76]. Furthermore, depletion of IRF6, a positively regulated Notch target, leads to decreased differentiation and increased tumor formation [77]. In this study, analysis of a panel of cutaneous SCC indicated a strong correlation between decreased expression of IRF6 and Notch and simultaneous increased expression of EGFR. Strikingly, a recent study using whole-exome and transcriptome sequencing identified mutations in *NOTCH1* or *NOTCH2* in roughly 75% of cutaneous SCC and SCC cell lines tested [78]. The majority of mutations were due to a G>A transition, typically attributed to UV damage, and resulted in loss of function. These findings not only demonstrate the power of next-generation sequencing in identifying critical mutations in disease, but also point to Notch as a novel biomarker for SCC as well as prioritizing it as a therapeutic target.

The Ras-MAPK pathway in multi-system syndromes

The evolutionarily conserved RAS-ERK/MAP kinase (MAPK) cascade functions to transduce extracellular signals to intracellular responses regulating cell proliferation, differentiation, and survival. Essential for normal tissue homeostasis, this pathway becomes pathologically dysregulated in many types of cancer, including via *RAS* gene mutations in 10% of human epidermal squamous cell carcinomas and the benign neoplasm nevus sebaceous (Figure 2), as well as in the so-called RASopathies, developmental disorders [79–82]. Attributed to germline mutations within this cascade, RASopathies often present with many interrelated phenotypic characteristics including facial dysmorphism, dermatological manifestations, cardiac abnormalities, and mental retardation (Figure 3) [82]. Thus, there has often been a failure to clinically differentiate each disorder, and recent work in this field has aimed at more distinct classifications to improve diagnostics and therapeutics.

The RASopathy Cardio-facio-cutaneous (CFC) syndrome is a result of mutations in the RAS-ERK/MAPK cascade including KRAS, BRAF, MEK1 and MEK2 [82]. Recent work has suggested that in spite of a variety of mutations, CFC patients might benefit from small molecular inhibitors of MEK as evidenced by observed responses to multiple inhibitors of MEK in both human cell lines and in developing zebrafish embryos characterized by varied mutant forms [83,84]. Phenotypically similar to CFC syndrome, Costello syndrome (CS) is characterized solely by mutations in HRAS [82,85]. Farnesylation inhibitors, which target posttranslational modifications of RAS, will be employed in a recently characterized mouse model for CS and should yield interesting therapeutic strategies [86].

Phosphoinositide 3-kinase pathway-related disorders

Phosphoinositide 3-kinase (PI3K)/Akt signaling, another important signaling pathway in the epidermis, protects differentiating keratinocytes from caspase-3 dependent apoptosis via engagement of epidermal growth factor receptor (EGFR) and Src families of tyrosine kinases with E-cadherin [87]. Phosphatase and tensin homolog (PTEN) negatively regulates the PI3K/Akt pathway and is mutated or deficient in a spectrum of sporadic cancers and hereditary cancer syndromes characterized by hyperproliferation and resistance to apoptosis [41]. **Cowden's** and **Bannayan-Zonana syndromes** are caused by germ line mutations in the tumor suppressor. Sporadic PTEN loss or mutations are associated with skin cancers including melanoma, SCC, and keratoacanthoma (KA). Aggressive SCCs with deletion in Grainyhead-like 3 (*GRHL3*), coding for a transcription factor required for normal epidermal homeostasis and differentiation, also displays PTEN deficiency and addiction to PI3K/Akt signaling [88]. However, in the context of activated Fos and PTEN loss, an increase in glycogen synthase kinase-3 β (GSK3 β) inactivation induces differentiation via p53 and/or p21^{Waf} cascade activation, thereby eliciting KA instead of SCC formation [89].

Concluding Remarks

Genetic disruptions in epidermal differentiation cause diseases that impact more than one in five persons. Increasing investigations into the genes affected in the resulting disorders has revealed some emerging organizing etiologic themes. Prominent among these are dominant signaling pathways, including the Notch, TGF β , IKK, Ras/MAPK, Phosphoinositide 3-kinase, p63, and Wnt signaling pathways as well as central biological processes that regulate calcium homeostasis, tissue integrity, cornification, and lipid biogenesis. The functional non-redundancy of genes impacted within these pathways and processes underscores their potential for therapeutic targeting. As the genetic basis for all human disorders of epidermal differentiation becomes established in the coming years, additional opportunities for effective therapeutic intervention that integrate affected pathways with newly discovered genetic alterations will emerge.

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Glossary

Corneocytes

terminally differentiated keratinocytes in the stratum corneum

Corneodesmosomes

specialized desmosomes that bridge corneocytes together

Cornification

transformation of keratinocytes into metabolically inactive corneocytes over a span of 2 weeks. The differentiation process is characterized by loss of organelles and nuclei and accumulation of keratin in terminally differentiated keratinocytes

Cornified Envelope (CE)

a structural layer of CE proteins in the stratum corneum that is irreversibly crosslinked by calcium-activated transglutaminases and essential in maintaining skin barrier function. CE proteins include loricrin, involucrin, late cornified envelope (LCE), and small proline-rich (SPRRs) proteins

Desmosomes

intercellular protein complexes composed of cell surface adhesion proteins linked to intracellular intermediate filaments for cell-to-cell adhesion

Desquamation

natural cycle of shedding and replacing corneocytes

Hyperkeratosis

thickening of the stratum corneum caused by keratin buildup resulting in abnormal thickening of the skin

KIF

keratin intermediate filament generated by assembly of keratin monomers form a structural component of the cell maintaining the overall cellular architecture

Ichthyosis

heterogeneous family of genetically inherited disorders characterized by defective desquamation resulting in the appearance of fishlike scales

Keratoacanthoma

considered a self-regressing variant of well-differentiated squamous cell carcinoma, appear as a symmetric, dome shaped tumor with a central depression filled with keratin debris

Lamellar bodies/granules

secretory organelles found in keratinocytes that are filled with lipids, enzymes, and protein and important for normal skin barrier function

Organotypic model

reconstitution of cell culture in a three-dimensional manner generating tissue resembling the organ of origin

Squamous cell carcinoma

cancer of epithelial origin frequently arising from sun-exposed regions of the skin

Figure 1. Epidermal differentiation and overview of disorders affecting differentiation

(a) Keratinocytes undergo a process of terminal differentiation involving stratification, which consists of the upward migration of keratinocytes from the basal layer containing progenitor cells into the spinous and granular layers; here, lamellar bodies provide the materials for formation of the impermeable epidermal barrier. (b) Mutations in keratin intermediate filaments 5 and 14 result in detachment from the basement membrane with disruption of the keratin intermediate filament network resulting in altered cytoskeletal architecture. (c) Mutations in components necessary for cell adhesion, such as corneodesmosome mutations exemplified here, result in increased intercellular spaces due to lack of cell-cell contact; mutations affecting this process of cornification result in defective barrier formation and dry, scaly skin. (d) Altered cell signaling can result in defective differentiation with increased proliferative capacity of basal progenitor cells, loss of cell adhesion, and the potential to become invasive squamous cell carcinoma.

Figure 2. Diseases of the epidermis

(a) Junctional epidermolysis bullosa features blistering and erosions at birth. (b) Lamellar ichthyosis is characterized by brown, tile-like scales over the entire body. (c) Ichthyosis vulgaris manifests as dry, scaly skin with diffuse general involvement. (d) Epidermolytic hyperkeratosis is characterized by recurrent blisters and hyperkerotic scales. (e) Nevus sebaceous presents as an orange plaque with pebbly surface. (f) Squamous cell carcinoma appears sharply demarcated and can present with erosions, scaling, and hyperkeratosis.

Figure 3. Mutations in the Ras/MAPK and PI3-K/Akt pathway in cutaneous disorders
 “RASopathies” are multi-system disorders characterized by epidermal phenotypes and typically resulting in tumor syndromes. Enumerated circles represent mutations observed in the following disorders: (1) Noonan syndrome exhibits mutations in *PTPN11* (SHP-2) and *KRAS*. (2) Cardio-facio-cutaneous (CFC) syndrome exhibits mutations in *KRAS*, *BRAF*, and *MEK*. (3) Costello syndrome exhibits mutations in *HRAS*. (4) LEOPARD syndrome exhibits mutations in *PTPN11*. (5) Neurofibromatosis contains mutations in *RasGAP*, *NF1*. (6) Legius syndrome exhibits mutations in *SPRED1*. (7) Banayan-Zonona and Cowden's syndromes contain mutations in *PTEN*. Phenotypes associated with these mutations are listed in Table 1.

Table 1
Epidermal disorders with associated genes and processes affected

Disease	Mutated Genes	Process Affected ^a	Phenotype
Pachyonychia Congenita	<i>KRT 6a, 16, 17</i>	IF	Hk, nail dystrophy
Epidermolytic Hyperkeratosis	<i>KRT1, KRT10</i>	IF	Blistering, Hk
Epidermolysis Bullosa Simplex	<i>KRT5, KRT14</i>	IF	Trauma-induced blistering with minimal scarring
Ichthyosis with Confetti	<i>KRT10</i>	IF	Blistering, Hk, pale confetti-like spots
Epidermolysis Bullosa Simplex-Ogna	<i>PLEC1</i>	BMZ Adhesion, Hemidesmosomes	Trauma-induced blistering
Junctional Epidermolysis Bullosa	<i>LAMA3, LAMB3, LAMC2, COL17A1, ITGB4, ITGA6</i>	BMZ Adhesion	Generalized blistering and erosions
Dystrophic Epidermolysis Bullosa	<i>COL7A1</i>	BMZ Adhesion	Generalized blistering of skin and erosions with scarring
Lethal Congenital Epidermolysis Bullosa	<i>JUP</i>	Desmosomes	Generalized blistering and erosions, alopecia, onycholysis
Palmoplantar Keratoderma	<i>JUP, PG, DSP, DSG1, KRT9, KRT16, KRT1</i>	CA, Desmosomes, IF	Hk affecting palms and soles, curly hair, arrhythmia
Neonatal Ichthyosis Sclerosing Cholangitis Syndrome	<i>CLDN1</i>	TJ	Sclerosing cholangitis, ichthyosis, hypotrichosis, dental abnormalities
Generalized Peeling Skin Disease	<i>CDSN</i>	Desmosomes	Pruritus, patchy peeling of entire skin
Netherton's Syndrome	<i>SPINK5</i>	Desmosomes	Hk, hair shaft defects
Exfoliative Ichthyosis	<i>CSTA</i>	CA	Scaly skin and peeling of non-erythematous skin on the palms and soles
Vohwinkel Syndrome	<i>LOR, GJB2</i>	CE, Gap Junction	Honeycomb Hk on palms and soles
Erythrokeratoderma variabilis	<i>GJB3, GJB4</i>	Gap Junction	Hk, transient patches of erythema
Ichthyosis vulgaris	<i>FLG</i>	CE	Dry, scaly, itchy skin covering entire body (Hk)
Lamellar Ichthyosis	<i>TGM1, ABCA12, ALOX12B, ALOXE3, ICHTHYIN, CYP4F22</i>	CE, FA & Chol. metabolism	Hk with scales and erythema covering entire body
Recessive X-linked Ichthyosis (RXLI)	<i>STS</i>	FA and Chol. metabolism	Large, brown scales covering limbs and trunk
Harlequin's Ichthyosis	<i>ABCA12</i>	FA and Chol. metabolism	Hk, severe form of congenital ichthyosis with grave prognosis
Darier Disease	<i>ATP2A2</i>	Ca ²⁺ signaling	Hk affecting the seborrheic areas
Hailey-Hailey Disease	<i>ATP2C1</i>	Ca ²⁺ signaling	Hk affecting the flexural areas
Ankyloblepharon-Ectodermal Defects-Cleft Lip/Palate	<i>TP63</i>	Transcription	Fusion of eyelids, epidermal erosion,

Disease	Mutated Genes	Process Affected ^a	Phenotype
			dystrophic nails, wiry hair, cleft lip/palate
Multiple Self-healing Squamous Epithelioma	<i>TGFBR1</i>	Signal transduction	SCC-like invasive tumors
Noonan Syndrome	<i>PTPN11, KRAS</i>	MAPK signaling	Heart, skeletal, hematologic and cognitive defects, distinctive facial dysmorphisms, Hk, lymphedema
Cowden's Syndrome	<i>PTEN</i>	PI3K/Akt signaling	Hamartomas of skin and mucosal surfaces
Cardio-facio-cutaneous (CFC) syndrome	<i>KRAS, BRAF, MEK1/2</i>	MAPK signaling	Heart and cognitive defects, distinctive facial dysmorphisms, Hk, sparse hair
Costello Syndrome	<i>HRAS</i>	MAPK signaling	Similar to CFC syndrome in addition to loose skin of hands and feet
Nevus Sebaceous	<i>HRAS</i>	MAPK signaling	Hairless plaque on scalp with distinct orange color and pebble-like texture
Pilomatricoma	<i>CTNNB1</i>	CA, Wnt signaling	Solitary hard, subcutaneous nodule

^aAbbreviations: IF, intermediate filaments; Hk, hyperkeratosis; BMZ, basement membrane zone; CA, cell adhesion; TJ, tight junction; CE, cornified envelope; FA, fatty acid; Chol., cholesterol.