

Genetic pathways in disorders of epidermal differentiation

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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, transforming growth factor β (TGF β), I κ B kinase (IKK), Ras/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), p63, and Wnt signaling pathways, as well as core biological 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 to guide development of future therapeutics to correct their dysfunction.

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 comprises self-renewing progenitor cells; the spinous layer, lying above the basal layer, comprises upward migrating, differentiating keratinocytes; the granular layer comprises cells producing the substrates necessary to form the impermeable barrier; and the stratum corneum comprises terminally differentiated enucleated lipid-embedded corneocytes (see [Glossary](#)) 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](#)).

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 (KRT5 and KRT14) are expressed in the basal layer of the skin and are replaced by keratins 1 and 10 (KRT1 and KRT10) 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 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* and *KRT5*) to the larger neutral-basic type II keratins (*KRT10* and *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

Glossary

Corneocytes: terminally differentiated keratinocytes in the stratum corneum.
Corneodesmosomes: specialized desmosomes that join 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 proteins in the stratum corneum that is irreversibly crosslinked by calcium-activated transglutaminases and is essential in maintaining skin barrier function. CE proteins include loricrin, involucrin, late cornified envelope (LCE), and small proline-rich (SPRR) proteins.

Desmosomes: intercellular protein complexes comprising cell surface adhesion proteins linked to intracellular intermediate filaments for cell-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.

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

Keratoacanthoma (KA): considered a self-regressing variant of well-differentiated squamous cell carcinoma, appears as a symmetric, dome-shaped tumor with a central depression filled with keratin debris.

Keratin intermediate filament (KIF): generated by the assembly of keratin monomers to form a structural component of the cell maintaining the overall cellular architecture.

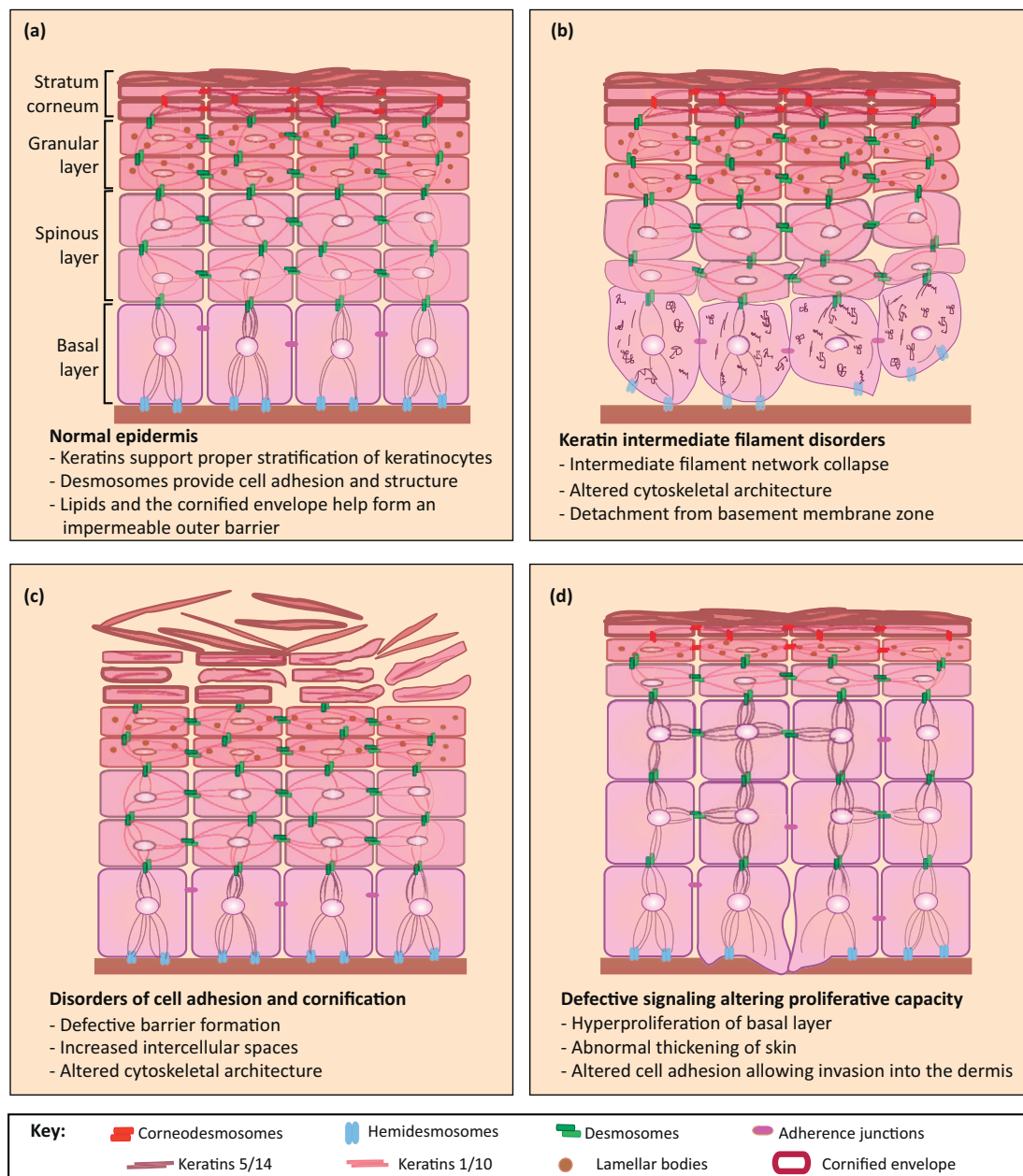
Lamellar bodies and/or granules: secretory organelles found in keratinocytes that are filled with lipids, enzymes, and protein, and are important for normal skin barrier function.

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.

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TRENDS in Genetics

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 and resulting in altered cytoskeletal architecture. **(c)** Mutations in components necessary for cell adhesion, such as the 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.

confirmed recurrent mutations in *KRT5/KRT14* and identified EB gene signatures that point to dysfunction in lipid metabolism as well as in epidermal keratinization [4]. EB is also characterized by mutations in various cell adhesion genes, including those encoding lamin 332, integrins, and collagen VII, recently reviewed in [5]. Among the mutations in EB associated with hemidesmosomes, a recent knock-in mouse model of EBS-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 ichthyosis, a skin disease initially characterized by redness and blistering, and later by the development of hyperkeratosis (Figure 2) [2,7]. Whereas deletion of *KRT10* in humans results in a severe skin

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