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Chapter

Keratinocytes in Skin Disorders: The Importance of Keratinocytes as a Barrier

Mayumi Komine, Jin Meijuan, Miho Kimura-Sashikawa, Razib MD. Hossain, Tuba M. Ansary, Tomoyuki Oshio, Jitlada Meephansan, Hidetoshi Tsuda, Shin-ichi Tominaga and Mamitaro Ohtsuki

Abstract

Keratinocytes are the major structural component of the epidermis. They differentiate from the basal through spinous to granular layers, and abrupt loss of nucleus pushes them to differentiate into cornified layers, which exfoliates as scales. Differentiation process is tightly controlled by the organized expression of transcription factors and other regulators, which sustains the physiological function of the skin barrier. The genetic abnormality of the molecules expressed in this pathway causes hereditary skin disorders and defects in barrier function. Ichthyosis is caused by keratins, enzymes, and structural proteins involved in lipid metabolism and cornified envelope formation. Atopic dermatitis seemed to be an immune-oriented disease, but the recent finding revealed filaggrin as a causative factor. Keratinocytes respond to acute injury by releasing alarmins. IL-33 is one of such alarmins, which provoke Th2-type inflammation. IL-33 works as a cytokine and, at the same time, as nuclear protein. IL-33 has double-faced nature, with pro- and anti-inflammatory functions. Epidermis, covering the entire body, should stay silent at minor insults, while it should provoke inflammatory signals at emergency. IL-33 and other double-faced molecules may play a role in fine tuning the complexed function of epidermal keratinocytes to maintain the homeostasis of human body.

Keywords: keratinocytes, keratin, mutation, ichthyosis, hereditary skin disorders

1. Introduction

Keratinocytes are the principal epidermal cells constituting the outermost layer of the skin—the external and largest organ of the human body. They are immunologically active in that they produce various cytokines and chemokines, stimulating dendritic cells and lymphocytes to trigger inflammatory skin diseases, as well as they respond to cytokines produced from immune cells to establish skin lesions of inflammatory skin diseases, such as psoriasis and atopic dermatitis. They are also very efficient in avoiding harsh environmental assaults, such as chemical, mechanical, radiological, and microbial insults. The
Keratinocytes protect the dermal homeostasis by having a constant turnover whereby the basal (inner) layer differentiates into the cornified (outer) layer. Thus, they form a constant and perfect outer barrier to the inner dermal layers and the body. They also form a rigid mechanical barrier by cornification—constructing a brick-and-mortar type of structure with cornified cells and lipids, the defects in either of which cause hereditary skin disorders upon mutation. They also secrete various antimicrobial peptides, such as cathelicidin, psoriasin, defensin, and many S100 proteins, to protect the skin from infection. The nuclei of keratinocytes contain various alarmins, such as HMGB1, IL-33, and IL-1alpha, which can induce rapid and strong inflammation upon injury, but also can get promptly inactivated by the enzymes present in the inflammatory environment. However, malfunctioning of the keratinocytes at its immunological level or at a genetic/protein level can lead to pathological conditions such as psoriasis, atopic dermatitis, and hereditary skin disorders.

Keratinocytes, as the main component of outermost epidermal layer, should provoke and at the same time stop inflammation at appropriate time points to maintain a stable and healthy condition of not only the skin, but also the entire body. Keratinocytes harbor anti-inflammatory properties more than other types of cells do, such as lymphocytes, macrophages, and dendritic cells, as keratinocytes are always exposed to environmental insults. The mechanism of developing inflammatory conditions has been intensely investigated; however, the mechanism of ceasing inflammation has not been fully investigated. I speculate that a novel approach to maintaining healthy conditions would be unraveled when the mechanism of sequestering inflammation is investigated and that epidermal keratinocytes are good candidates to investigate these mechanisms because they present pro- and anti-inflammatory properties in vivo and in vitro.

In this chapter, various cutaneous disorders have been discussed with emphasis on keratinocyte function and roles in pathogenesis. We have surveyed PubMed with each disease name, picked up the original literature with pivotal findings, reviewed articles covering the related area of interest, and wrote this chapter.

2. Epidermal keratinocytes

Epidermal keratinocytes form a stratified epithelium, consisting of basal, spinous, granular, and cornified layers starting from the dermal side. Epidermal keratinocytes exert their functions through structural components such as actin, microtubules, keratin filaments, desmosomes, hemidesmosomes, tight junctions, and adherent junctions; their motility, proliferation, and cytokine production being controlled by these structural proteins. Epidermal keratinocytes gradually differentiate through the layers—from the basal, spinous, and granular, ultimately to the cornified cell layer. They demonstrate various characteristic features owing to their differential function and according to their differentiation state, which are sometimes more complex than those of simple epithelial cells constituting the digestive tract and glands [1].

The primary and most important function of epidermal keratinocytes is their role as a physical barrier of the skin, in addition to their role as a responder to the external stimuli. The cornified cells, together with inter-cornified cell lipids, form cornified cell barriers to protect the inner body from harsh external environmental stimuli. The cornified cells, upon catalysis by transglutaminase 1, form a cornified cell envelope—a strong structure composed of filaggrin that aggregates keratin filaments, with various protein components such as involucrin, loricrin, SPR, and desmosomal proteins. Defects in the enzymes and protein components essential in
Recent findings have revealed that some patients with atopic dermatitis (AD) harbor loss-of-function mutations in the filaggrin gene, resulting in severe skin barrier defects. Ichthyosis vulgaris (IV) is also caused by mutations in the filaggrin gene, but patients with this mutation develop either AD, IV, or both, indicating that mutations in the filaggrin gene alone are not enough to determine the phenotypes [4–7]. Mutations in the transglutaminase 1 gene and other genes important in the cornification processes, such as ATP-binding cassette subfamily A member 12 (ABCA12), and arachidonate 12-lipoxygenase 12 s type (ALOX12), cause hereditary ichthyosis, also known as acquired recessive congenital ichthyosis [8]. Connexin is a component of the gap junction, and mutation in gap junction protein beta 3 (GJB3) gene, which encodes connexin (Cx31) causes erythrokeratoderma variabilis, in which inflammatory erythematous eruptions with hyperkeratinization gradually change its form [9]. Mutations in the loricrin gene cause loricrin keratoderma, with characteristic finger constriction ring formation or congenital ichthyosiform erythroderma [10, 11].

Steroid sulfatase is an enzyme that catalyzes the degradation of cholesterol sulfate, a molecule that functions in the attachment of cornified cells. The mutation in its gene causes X-lined ichthyosis, with retarded detachment of cornified cells, termed as retention hyperkeratosis. Point mutations result in typical skin manifestations; whereas, mutations spanning bigger lengths of this gene involving the surrounding genomic region are accompanied by other syndromic symptoms, such as mental retardation, short stature, and epilepsy [12].

Figure 1. Characteristic skin manifestation in hereditary skin disorders with mutation in genes expressed in keratinocytes. a) Bulla formation on the foot of a child having epidermolysis bullosa simplex (EBS) and with mutation in the KRT5 gene. b) Macular brownish pigmentation in EBS with mottled pigmentation in patients with mutation in KRT5 gene. c) Hyperkeratosis in hands, d) nail deformity and e) dental decay in patients with dystrophic EB and with mutation in the integrin beta 4 gene. f) Diffuse hyperkeratosis in hands, with lichenification in wrist, g) hyperkeratosis with lichenification in cubital fossa, h) small bulla formation on diffuse erythema and i) its histopathology with hematoxylin and eosin staining in patients with Epidermolytic hyperkeratosis and mutation in KRT1 gene.
### Common Ichthyosis

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<thead>
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### Autosomal recessive congenital ichthyosis

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<td>TGM1, NIPAL4, ALOX12B, ABCA12</td>
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<td>AR</td>
<td>ALOXE3, ALOX12B, ABCA12, NIPAL4, TGM1, CYP4F22</td>
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### Keratinopathic ichthyosis

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### Autosomal ichthyosis syndrome

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<tr>
<td>Netherton syndrome</td>
<td>AR</td>
<td>SPINK5</td>
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Some hereditary keratinizing disorders are accompanied by syndromic symptoms other than skin manifestations. Mutations in GJB2 gene, encoding Cx26, cause KID syndrome—with keratitis, ichthyosis, and deafness as triads, exhibiting papillomatous and spinous keratotic eruptions on the face and extremities, and with palmoplantar keratoderma and alopecia [13]. Mutation in the serine protease inhibitor SPINK5 causes Netherton syndrome, with atopic dermatitis-like skin eruptions, characteristic ichthyosis linearis circumflexa and bamboo hair [14]. Sjogren-Larsson syndrome is caused by a mutation in the fatty aldehyde dehydrogenase (ALDH3A2) gene, with clinical symptoms including ichthyosis, spastic limb paralysis, and mental retardation [15]. Figures 1 and 2 shows skin manifestations of several hereditary skin disorders. Table 1 shows a summary of the types of ichthyosis and their accompanying gene mutations.

### 3. Keratinopathies

Keratins are the main intermediate filaments of epidermal keratinocytes. The keratin family consists of more than 50 members; acidic keratin and basic keratin monomers pair to form heterodimers, which are then organized into tetramers with an anti-parallel alignment. Tetramers of keratins are stored at the peripheral boundaries of cells for filament formation when needed. Lateral and longitudinal aggregations of these tetramers and octamers form keratin filaments. Local pH, osmotic conditions, and phosphorylation status are thought to be the driving forces of filament formation [16].

Simple epithelia consist of simple epithelial keratins, such as K8, K18, and K19. Basal cells of the simple and stratified epithelia express K5 and K14, while the suprabasal cells express K1 and K10 in the interfollicular epidermis, K3 and K12 in the corneal epithelium, K4 and K13 in the esophageal epithelium, and K6 and K16 in the oral epithelium. The follicular epidermis and palmoplantar epidermis express K6, K16, and K17. Their expression is tightly controlled by transcription factors in a differentiation- and localization-dependent manner.

Mutations in keratin genes cause various hereditary skin disorders [17]. Mutations either in KRT5 and KRT14 gene cause epidermolysis bullosa simplex (EBS), manifested by bulla formation with slight mechanical forces from childhood. KRT1 or KRT10 gene mutations cause epidermolytic ichthyosis (EI), with characteristic histopathological features called epidermolytic hyperkeratosis characterized by large droplets of keratohyalin granules with vacuolization and hyperkeratosis in epidermal keratinocytes. A similar mutation in the KRT9 gene causes Voermer-type palmoplantar keratoderma (PPK), with similar epidermolytic hyperkeratosis on the palm and soles, owing to the exclusive KRT9 expression and distribution on palms and soles in humans. Similarly, a mutation in the KRT2e, expression of which is distributed in the granular layer of the epidermis, causes superficial epidermolytic ichthyosis. Pachyonychia congenita, manifested by thickening of finger and toenails and sometimes accompanying steatocystoma...
multiplex, is caused by mutations in \textit{KRT6}, \textit{KRT16}, or \textit{KRT17}, which is expressed in nails and follicular epithelium [18]. White sponge nevus usually seen in the oral epithelium is caused by mutations in the \textit{KRT4} or \textit{KRT13} gene, with whitish, somewhat keratinized oral epithelium showing papillomatous growth [19]. Simple epithelial keratins, such as \textit{KRT7}, \textit{KRT8}, \textit{KRT18}, and \textit{KRT19}, are distributed not only in cutaneous glandular structures, such as sweat glands and sebaceous glands but also in various internal organs, including the digestive tract and liver. Mutations of these simple epithelial keratins in skin disorders have not yet been elucidated, but the importance of \textit{KRT8} and \textit{KRT18} mutations in liver diseases have been postulated. End-stage liver disease patients have been reported to show higher rates of \textit{KRT 8/18} mutations [20]. The solubility of keratins depends on their phosphorylation status, and mutations in the phosphorylation site affect the solubility of keratin filaments, resulting in cell damage. Recent findings revealed that the phosphorylation of keratins is also affected by the acetylation or methylation status of keratins; thus, mutations at these sites also cause cell damage. Mutations in \textit{KRT8} and \textit{KRT18} affect the keratin phosphorylation, acetylation, or methylation, in turn, affecting the stability in keratin filaments, resulting in an imbalance between \textit{KRT8} and \textit{KRT18} proteins, and causing excessive oxidative stress and susceptibility to liver disorders [21, 22].

4. Adherence machinery of epidermal keratinocytes

Adherence machinery is indispensable for controlling keratinocyte cell motility, proliferation, and viability, as well as the epidermal barrier function by controlling cell attachment and cell tension. Keratinocytes have six major adherence mechanisms [23, 24]: 1) Hemidesmosomes, which connect basal keratinocytes to the dermal component, with cytoskeletal molecules such as keratins, 2) desmosomes, which connect neighboring keratinocytes, sustain the epidermal sheet structure and maintain tension by connecting to cytoskeletal molecules, such as keratins, 3) Adherence junctions, which control keratinocyte motility by connecting intracellular actin to E-cadherin in the adherence junctions to neighboring keratinocytes [25], 4) Gap junctions, which also have ion-transporter functions, indirectly control keratinocyte barrier function, 5) Tight junctions, which control the liquid interface in epithelia and consist of claudins and occludins [26], and 6) Focal adhesion—attachment of plaques connecting cells to the extracellular matrix, thereby, making connections to scaffolds to maintain the keratinocyte motility, proliferation, and viability.

Hemidesmosomal proteins are indispensable for maintaining normal dermal-epidermal structures (Figure 3) [27, 28]. Mutations in hemidesmosomal protein genes, such as integrin alpha 6 or beta 4, cause junctional epidermolysis bullosa [29]. Mutations in plectin, a constituent of desmosomes and hemidesmosomes, cause junctional type epidermolysis bullosa with pyloric atresia [30]. Collagen type VII localizes from just beneath lamina densa to support attachment of lamina densa to the dermal structure. Mutations in the collagen type VII gene cause dystrophic epidermolysis bullosa with prominent skin ulcer and scar formation [31, 32]. These severe EBs usually occur in patients with homozygous mutation or compound heterozygous mutations. A heterozygous mutation, the same mutation but which harbors on only one allele of the gene, causes a milder form of EB, leading to the development of nodular prurigo-like lesions or scar formations in autosomal dominant type dystrophic EB or development of palmoplantar keratoderma with alopecia and dental deformation in autosomal dominant type junctional EB. A
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DOI: http://dx.doi.org/10.5772/intechopen.103732

A recent study revealed that mutations in desmoplakin cause lethal acantholytic epidermolysis bullosa [33].

5. Skin barrier dysfunction in diseases

Atopic dermatitis patients present decreased filaggrin and ceramide contents in their cornified layers, along with decreased skin barrier function [34]. This dysfunctional barrier allows allergens to penetrate the skin, thus, resulting in sensitization to environmental allergens [35]. Peanut allergies are often observed in infants of families that consume large amounts of peanut and have detectable levels of peanut debris in the surrounding environment [36]. Exercise-induced food allergy also develops in relation to filaggrin mutation [37]. A previous study has shown that infants with frequent emollient hydration of skin showed a lower rate of bronchial asthma development compared to babies without emollient hydration of skin, indicating the importance of the skin barrier functioning in maintaining overall health and stable homeostasis [38]. Figure 4 illustrates the epidermal structure with barrier proteins.

Mutations in filaggrin and protease inhibitors can cause atopic dermatitis. Netherton syndrome is caused by a mutation in the serine protease inhibitor KAZAL type5 (SPINK5), which results in atopic dermatitis-like skin eruption [39]. Nagashima-type PPK is caused by a mutation in SERPINB7, a serine protease inhibitor, with low-grade hyperkeratosis on the palms and soles, involving the backside of the fingers, toes, and a triangular lesion on the wrist. Some cases of Nagashima-type PPK also develop food allergies or atopic dermatitis [40]. Protease inhibitors are essential for stopping the catalyzing reaction by proteases, thus, protecting the skin barrier from over-degradation. The precise mechanisms underlying the development of atopic dermatitis or allergy in Nagashima-type PPK patients are not clear, but one theory is that proteinase activation receptors are potent pro-inflammatory...
Figure 4. The structure of epidermis and its adhesion molecules. a) Schematic view of epidermis structure and its adhesion molecules. Basal keratinocytes attach to basement membrane through hemidesmosomes, having keratins such as KRT5 and KRT14. Suprabasal keratinocytes start to produce KRT1 and KRT10 and attach to neighboring keratinocytes with desmosomes. Granular layer cells express KRT1 containing keratohyalin granules and attach to the neighboring cells with tight junctions, which also have desmosomes. Corneocytes lose nuclei and embed in lipid layers, connecting each other with corneodesmosomes. Cornified cell envelope develops when cells become corneal layer cells from granular layer cells. Adherence junctions exist from basal keratinocytes to granular layer keratinocytes. b) Cornified envelope development from its components. Filaggrin aggregates keratin filaments and involucrin, and other cornified envelope proteins gather to form a cornified cell envelope, upon catalysis by transglutaminase 1.

molecules that react with proteinases to induce inflammation. Thus, protease inhibitors could be a therapeutic target for atopic dermatitis [41].

Lipid abnormalities could be another cause of atopic dermatitis, demonstrating the skin barrier dysfunction. A decrease in ceramide content of the cornified layer has been demonstrated in patients with atopic dermatitis, which is another cause of skin barrier dysfunction [42]. Ceramide constitutes almost 50% of the lipids in the corneal layer and is indispensable for skin barrier function. Mutations in genes involved in lipid metabolism are not known in atopic dermatitis, but gene metabolic diseases, such as Gauche disease and Nieman-Pick disease that are characterized by mutations in the glucocerebrosidase and sphingomyelin phosphodiesterase 1 gene, respectively, which are indispensable in ceramide synthesis, resulting in development of atopic dermatitis-like skin eruptions from early childhood. Abnormalities in lipid metabolism could be another cause of atopic dermatitis, which requires further investigation [43].

Skin barrier function is affected not only by genetic conditions but also by ordinary routines of daily life. People who often scrub too much during bathing, bathe for a long time period or very frequently, and especially those who scrub their skin with nylon towels or scrubbing brushes show very dry skin with small scales all over the body. These individuals often complain of severe itching, especially after bathing, often resulting in eczema development. Excessive use of detergent also causes barrier disruption by increasing the pH of the skin, resulting in enhanced enzymatic activity of proteinases in the cornified layers [44]. These lifestyle routines would exacerbate eczematous changes in individuals having a genetic predisposition that makes them more susceptible to barrier disruption.

Keratinocytes form not only mechanical barriers but also chemical or immunological barriers for humans. They express several antimicrobial peptides, such as cathelicidin, defensin, psoriasin, and various S100 proteins. These antimicrobial peptides prevent pathogenic microbes from colonizing the skin surface, thus
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conferring resistance to microbial infections [45]. Certain conditions such as atopic dermatitis have decreased production of antimicrobial peptides, leaving the individuals more susceptible to bacterial or viral infections through the skin [46, 47]. Filaggrin mutations are at times the direct cause of barrier disruption, but T helper (Th)2-skewed immune conditions can be another cause too, as Th2 type cytokines cause a less differentiated state of keratinocytes thus resulting in lower production of antimicrobial molecules and barrier proteins [48]. Mutations in filaggrin also cause ichthyosis vulgaris, which often co-exists in atopic dermatitis patients. However, not all patients with atopic dermatitis have ichthyosis vulgaris and vice versa, even in the presence of filaggrin gene mutations [7]. Thus, the filaggrin mutation alone cannot explain the pathogenesis of atopic dermatitis.

Psoriasis is another major inflammatory skin disorder that shows hyperproduction of antimicrobial peptides in the epidermis induced by skewed Th17 populations thus making patients resistant to skin infections [49, 50]. Cathelicidin—one of the antimicrobial peptides, complexes with self RNA or DNA to induce the activation of myeloid dendritic cells and plasmacytoid dendritic cells, respectively. This activation further triggers psoriatic inflammation, thus creating a positive feedback loop in pathogenesis of psoriasis [51, 52]. Recent advancements in translational research produced many “biologics”, which target inflammatory cytokines, such as IL-17, TNF, and IL-23, as a treatment option for psoriasis. These include anti-TNF antibodies (adalimumab [53], infliximab [54], certolizumab-pegol [55]), anti-IL-17 antibodies (secukinumab [56, 57], ixekizumab [58], brodalumab [59], bimekizumab [60]), anti-IL-12/23p40 antibody (ustekinumab [61, 62]), and anti-IL-23p19 antibodies (guselkumab [63], risankizumab [64, 65], thildrakizumab [66–69]).

Janus kinases (JAKs) are important intracellular signaling molecules downstream of cytokine receptors [70]. They are also deeply involved in inflammation in psoriasis, and JAK inhibitors have been developed as therapeutic options in psoriasis [71–76]. Ichthyosis has also been shown to have a Th17-skewed immune balance [77], and Th17 is a potent inducer of antifungal immunity. However, ichthyosis patients often develop cutaneous superficial fungal infections [78, 79]. Taken together, this suggests that the immune imbalance by itself cannot explain the susceptibility to fungal infections, meanwhile also implicating the importance of proper functioning of the skin barrier to avoid superficial fungal infections.

6. Danger signals from keratinocytes

As a barrier, keratinocytes respond to emergency conditions by releasing danger-associated molecular patterns (DAMPs) when acutely injured. IL-33 is one such emergency molecule, which resides in the nucleus in a steady-state, but is released when cells undergo necrosis to stimulate immune reactions [80]. IL-33 is a relatively recently identified member of the IL-1 family and functions mainly as a pro-inflammatory molecule, although under certain conditions, it can also work as an anti-inflammatory molecule. IL-1 alpha—the prototype of IL-1 family members, was identified as an alarmin several decades ago. The Koebner phenomenon in psoriasis is attributed to the release of IL-1 alpha from damaged keratinocytes, which induces psoriasis in regions after skin injury [81]. IL-1 alpha is an interesting cytokine that mainly functions as a soluble cytokine, but also shows a nuclear presence. It has been reported that IL-1 alpha repeatedly travels between the cytoplasm and nucleus, and is released into the extracellular space upon cell damage to provoke inflammation [82]. IL-33 has similar characteristics in that it resides in the nucleus too, is released during cell necrosis, and induces inflammation. IL-33, similar to IL-1 beta, is produced as a full-length pro-form. IL-33 pro-form is active, but even
more, activated when digested by neutrophil elastases or cathepsin. It is, however, inactivated when digested by caspases, unlike IL-1 beta, which is activated by caspases during activation of NLRP3 inflammasomes. ST2L—a receptor of IL-33, is expressed on Th2 cells, group 2 innate lymphoid cells, and regulatory T cells, and its soluble form—sST2, blocks the interaction of IL-33 with ST2L [83].

IL-33 exhibits both pro-inflammatory and anti-inflammatory roles. As a Th2 cytokine, it stimulates ST2L-expressing cells, including mast cells, Th2, and ILC2 cells. This enhances Th2 type inflammation by inducing expression of Th2 type cytokines, such as IL-5 and IL-13. However, upon Th1 or Th17 activation, IL-33 may attenuate pathological conditions by skewing Th2 type inflammation. The graft versus host disease (GVHD) reaction [84] was reported to be attenuated by IL-33, and experimental autoimmune encephalomyelitis showed reduction in response to IL-33 action [85]. Graft rejection in heart transplantation was reported to be attenuated by treatment with IL-33 [86]. IL-33, by inducing regulatory T cell function, was shown to induce immunosuppression [87]. UVB-induced immunosuppression too has been shown to be attributed with IL-33 [87]. Immune dysregulation in coronavirus infection is hypothesized to be caused by the IL-1 family member of cytokines [88]. IL-33 has also been shown to induce neutrophilic infiltration in several animal models and disease conditions, which may be interpreted as a pro-inflammatory effect [89].

IL-33 has dual nuclear and soluble cytokine forms. Nuclear IL-33 functions as a transcriptional regulator. In acute wound healing processes, IL-33 functions by attenuating inflammation by affecting the NF kappa B activity and enhancing wound healing [90]. On the other hand, IL-33 as a cytokine enhances immune reactions in decubitus ulcer models (unpublished). Both IL-33 and IL-1 alpha, when in the nucleus, bind to chromatin and are not released easily, thus, forming a reservoir for inflammatory signals. The regulation of nuclear or cytoplasmic localization of IL-33 is not clear but maybe dependent on its nuclear localization signal. Tsuda et al. [91] revealed that there are several different forms of splice variants of naturally occurring IL-33, of which expression is regulated by distinct promoters [92]. These splice variants should have distinct roles, which could regulate the pro- or anti-inflammatory properties of IL-33.

In the steady-state, keratinocytes should remain silent as a constitutively active state could result in excessive inflammation, which in turn can harm the overall human health. Cultured keratinocytes usually require higher concentrations of cytokines to provoke inflammatory signals; for example, keratinocytes need TNF in the range of several ng/ml to produce inflammatory cytokines, while dendritic cells or lymphocytes require only several pg/ml of the same cytokine to produce an inflammatory effect to the same or even a greater extent [93, 94]. Keratinocytes by differentiating to cornified cells become resistant to environmental stimuli, such as UVB; i.e., they usually respond sensitively to UVB in monolayer culture, but they become resistant to UVB stimulation when they differentiate in 3D-culture [95]. Some chemokines, such as MIP3 alpha/CCL20 are produced more in suprabasal cells than from basal cells [96], but production of IL-1 receptor antagonist is enhanced when keratinocytes are differentiated [97], which may result in attenuation of inflammatory response in differentiated keratinocytes. IL-33 and IL-1 alpha, more clearly expressed in suprabasal cells [98], when in the nucleus bind to chromatin not to be released easily, thus forming the reservoir for inflammatory signals.

7. Conclusion

Epidermal keratinocytes protect humans from the outer environment by forming an efficient mechanical, chemical, and antimicrobial barrier. Mutations
in various molecules present in the keratinocyte can cause hereditary disorders. The keratinocyte structure is maintained by many structural molecules, including keratins, actin, microtubules, and associated proteins and adhesion molecules. The barrier function depends on these structural molecules, as well as other antimicrobial and immunological components, such as infiltrating or resident immune cells, such as lymphocytes, dendritic cells, and macrophages. At the same time, keratinocytes are resistant to stimulation in comparison to other cell types, such as lymphocytes and dendritic cells, as shown in some pieces of literature that they respond to the same stimuli with much fewer attitudes compared to immune cells. IL-33, an alarmin released during insults into the skin, works as an alarmin to provoke inflammation, but at the same time often attenuates inflammation by activating regulatory T cells and skewing Th2 mediated inflammation. This relative unresponsiveness and dual-faced character with pro- and anti-inflammatory properties would be the characteristics of keratinocytes, which cover the entire body by facing environmental stimuli all the time. Thus, the differentiation and structural characteristics of epidermal keratinocytes prevent the skin from hypersensitivity to environmental stimuli.

The mechanism of developing inflammatory conditions has been intensively investigated, but the mechanism by which the inflammation status returns to the steady-state, or how inflammatory status remains under control to prevent excessive inflammation in healthy humans has not been fully investigated.

A novel approach to maintaining healthy conditions would be unraveled when the mechanism of sequestrating inflammation and returning to normal steady-state condition is investigated. Epidermal keratinocytes are good candidates to investigate these mechanisms because they present both pro- and anti-inflammatory properties in vivo and in vitro.

Acknowledgements

I thank all the members of our department for participating in clinical and basic research on patients.

Conflict of interest

The authors declare no conflict of interest.
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Keratinocytes in Skin Disorders: The Importance of Keratinocytes as a Barrier
DOI: http://dx.doi.org/10.5772/intechopen.103732

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