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Chapter 2

Regulation of Expression of Keratins and their Pathogenic Roles in Keratinopathies

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Abstract

Keratins are the epithelia-specific members of intermediate filament superfamily and consist of 54 members. They serve primarily as cytoskeletons, which sustain cell structures. They also influence on cell proliferation and motility by rapidly changing their morphology and distribution through post-translational modification. The expression of keratins genes is regulated by various cytokines and growth factors, mainly through distinct transcription factors. Mutations in keratin genes cause various cutaneous diseases as well as predisposition to inflammatory disorders of internal organ, such as the intestine and the liver. Keratins directly interact signaling molecules, which affects inflammatory processes, and cancer progression. The mechanism of keratin involvement in many diseases will be elucidated in future, which would help identifying novel target for treatment.

Keywords: inflammation, mechanical stress, expression regulation, keratinopathies, keratin

1. Introduction

Keratins are the epithelial-specific members of intermediate filament superfamily, which constitutes the cytoskeleton of cells consisting epithelial tissues, such as stratified epithelia, simple epithelia, hair and nails. Keratin family constitutes with 54 distinct proteins, 28 type I and 26 type II keratins, which expression is tightly regulated in a pairwise fashion. The expression of keratins is site-, differentiation- and context-dependent. Keratin sustains cell-architecture by serving as cytoskeleton, and also it is involved in regulation of cell metabolism and signaling, thereby influencing cell proliferation, migration and apoptosis [1].

Mutation in keratins causes hereditary keratinizing disorders and bullous diseases, such as ichthyosis, palmoplantar keratoderma and epidermolysis bullosa simplex, called "keratinopathies". Mutated keratins cause disruption in cytoskeleton and induce collapse in cell structure. Pathogenic mutations in keratins, which cause epidermolytic ichthyosis and epidermolytic palmoplantar keratoderma, are responsible for hyperkeratosis and inflammation in skin, enhanced by environmental stimuli such as mechanical stress, infection and oxidative stress. Recent studies revealed the role of keratins other than as structural protein in these disorders [2].

Many studies have been performed to reveal the role of keratins in physiological and pathological state, which are far more abundant to follow in this chapter. In this chapter, the role of keratins in physiological state is reviewed and the mutations in keratin genes causing keratinopaties are focused concisely.

2. Keratins

Keratins are the member of intermediate filaments (IF), which composed of six subtypes (**Table 1**) [3]. IFs, 10 nanometer wide filamentous proteins, first described by Holtzer et al. [4] in muscle cells are cytoskeletal proteins constituting almost 70 genes, among which 54 are keratins. Keratins share the structure with other IFs, composed of three domains; a central α-helical rod domain with non-helical head and tail domain containing many phosphorylation sites (**Figure 1**). Keratins have a property of self-assembly, which form filamentous structure. Type I and Type II keratins make heteropolymers, which further form keratin filaments. Type I keratins are acidic, low molecular weight, consists of K9–K40, while type II keratins are basic or neutral, high molecular weight proteins, consists of K1–K8, K71–K86. Expression regulation of each keratin is dependent on tissue-type, differentiation status, and is context-dependent. Keratins are divided into three groups. One is "simple" keratins, expressed in embryonic, and one-layered epithelia, including hepatocytes, intestinal

Subtype	Proteins	Specificity
Type I	Keratins, acidic	Soft stratified epithelia (skin, esophagus, oral mucosa etc.), Soft simple epithelia (gut, sweat gland, etc.), hard epithelia (hair, nail, oral papillae)
Type II	Keratins, basic	
Type III	Vimentin, desmin, glial fibrillary acidic protein, peripherin, syncoilin	Vimentin: mesenchymal cells, desmin: muscle cells, GFAP: astrocytes, glia, peripherin: C-fiber neuron, syncoilin: muscle cells
Type IV	Neurofilament-L, M, H, internexin, synemin, nestin	Neurofilament, internexin: neurons, synemin: muscle cells, nestin: undifferentiated neural cells, neural stem cells
Type V	Lamins A, B, C	Nuclear membrane
Orphan	Filensin, phakinin	Lens

Table 1. Classification of intermediate filament.

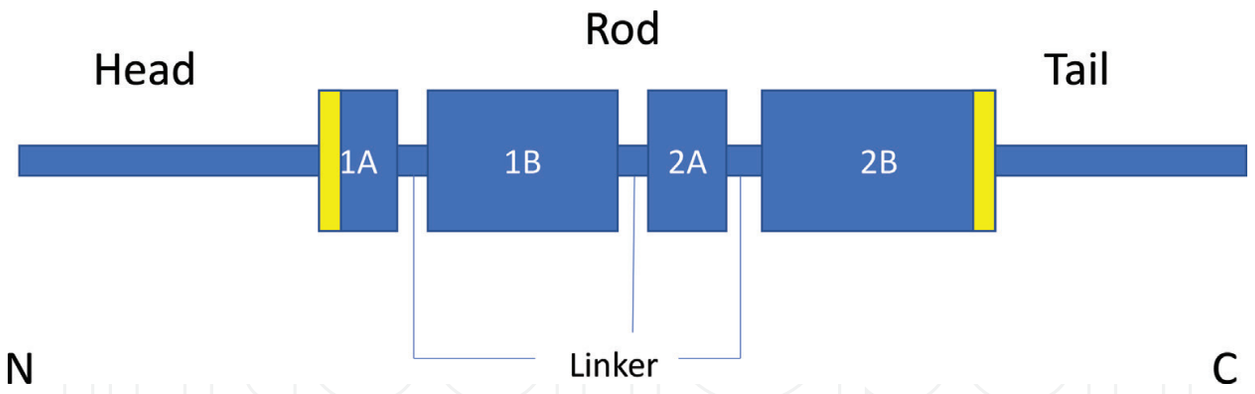

Figure 1. The structure of keratin protein: Central rod domain with head and tail region. Keratin protein consists of rod domain with 4α-helical segments (1A, 1B, 2A, 2B) interconnected with three linker domains, and non-helical head and tail domains. Most of the disease-causing mutations in epidermal keratins occurs in helix initiation and termination motifs at the periphery of 1A domain and 2B domain (indicated with yellow color).

epithelia and sweat glands. "Barrier" keratins are expressed in stratified squamous epithelium, such as skin, oral mucosa and esophagus. "Structural" keratins are hard keratins, constituting hair and nails [3].

Keratin filaments are observed as tonofilaments under electron microscope, which converge at desmosomes and hemidesmosomes. Desmosome is an attachment apparatus between epidermal keratinocytes located at the plasmamembrane of lateral and upper side of basal epidermal keratinocytes, and at all the surrounding plasmamembrane of suprabasal epidermal keratinocytes. Hemidesmosome is an attachment apparatus which conjugates basal keratinocytes to basement membrane, located at the bottom of the basal keratinocytes. These attachment apparatus have a distinct structure. Desmosomes are composed of transmembrane cadherins such as desmogleins, armadillo proteins such as plakoglobins and plakophilins, and plakins such as desmoplakin and plectins which link intracellular desmosomal plaque to keratins (**Figure 2**). Hemidesmosomes composed of integrin $\alpha 6$ and $\beta 4$, which link hemidesmosomes to laminin, bullous pemphigoid antigen (BPAG)1 and 2, and plectin, which mediate interaction of keratin intermediate filaments to integrins (**Figure 3**). Plectin and desmoplakin anchor keratin filaments to intracellular hemidesmosomal and desmosomal plaque, respectively. Plectin also links keratin filament to nuclear membrane, thus forming cytoskeletal architecture in epidermal keratinocytes [3]. Focal adhesion is another type of adhesion machinery, connecting cells to extracellular matrix (ECM) involving integrins, and anchor actin filaments.

The filament-junction-nucleus network sustains cell structure and rigidity, and anchor cells in three-dimensional architecture of epithelium. The epithelium, however, constantly turnover, regenerates itself when injury, and proliferates at inflammation. Keratin cytoskeleton should be flexible, plastic and dynamic when cells proliferate and migrate. Recent studies revealed how keratin filaments assembles and disassembles in cells. Keratin filament assembly starts at periphery of the cell, close to focal adhesions. In migrating cells, many keratin particles are formed in the lamellipodia where focal adhesions are abundant, which assembles to form keratin filament precursors (KFP). Oligomers of keratin particles are added equally to both ends of KFPs, which become larger in size, and when they approach to the keratin filament

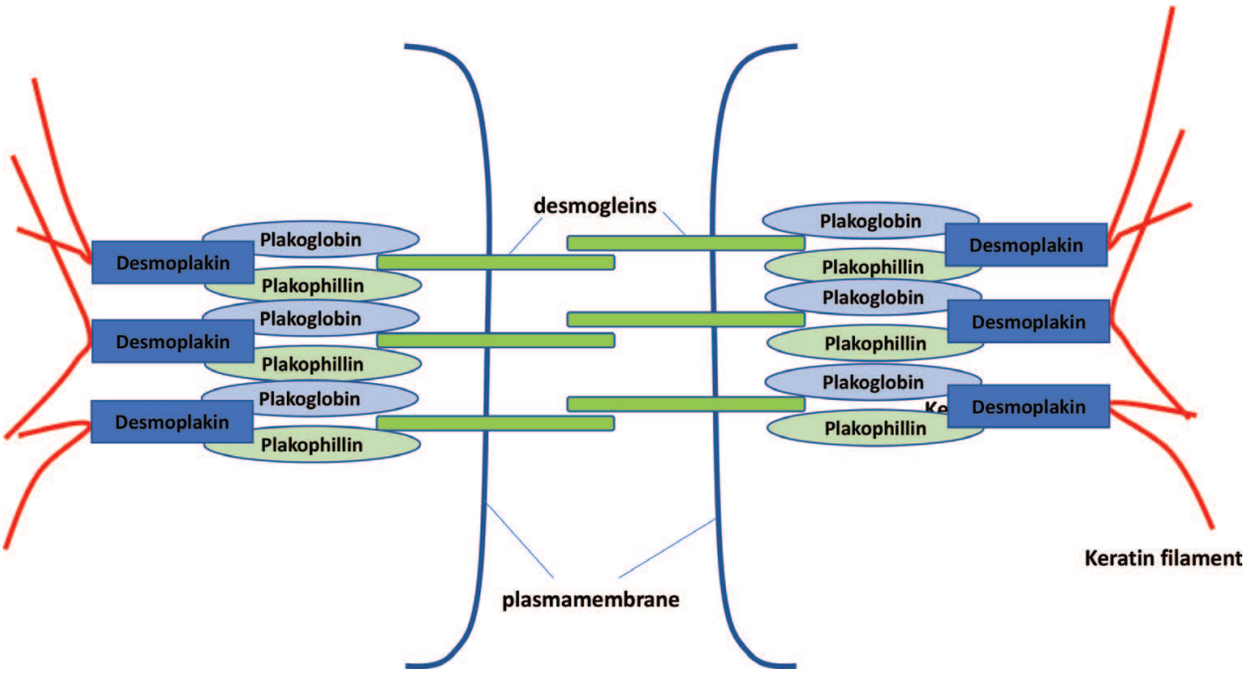

Figure 2. The structure of desmosome.

network close to the nucleus, KFPs integrate in the network adding another branch to the keratin filament network. Keratin filaments further assembles to form bundles close to the nucleus. This assembly of keratin occurs in centripetal flow, while the disassembly occurs close to the nucleus. This "keratin cycle" provides more efficient way over degradation and de novo biosynthesis, and similar recycling system has been observed in other cytoskeletal components, such as actin, and microtubles [5].

Keratins undergo various post-translational modifications, such as phosphorylation, ubiquitination, sumoylation, and acetylation, which regulate the solubility of keratins at specific conditions. Ubiquitination of keratin filaments and subsequent proteasomal degradation have been described as disassembly process. Also, phosphorylation is involved in dissociation of soluble non-filamentous form of keratins. Inhibition of p38 mitogen associated protein kinase (MAPK), or protein kinase C (PKC) ζ results in increased stability, while increased kinase activities result in enhanced keratin filament turnover.

Many phosphorylation sites have been identified on simple epithelial keratins, but fewer in epidermal keratins. Keratin 8 and 18 are phosphorylated when cells are stimulated with sheer stress through protein kinase C(PKC)ζ.

Keratin filament network supports mechanical resilience of the cell, especially for cells of barrier tissues, such as epidermis. Desmosomes and hemidesmosomes, the attachment apparatus of keratinocytes, convey mechanical stress signal to keratins, and to nucleus. When cells become migratory, desmosome-dependent cell–cell adhesion becomes weaker, with reduced co-localization of desmosomes with keratin filaments. Complete knockout of keratin filaments caused scattered distribution of hemidesmosome components, faster attachment to

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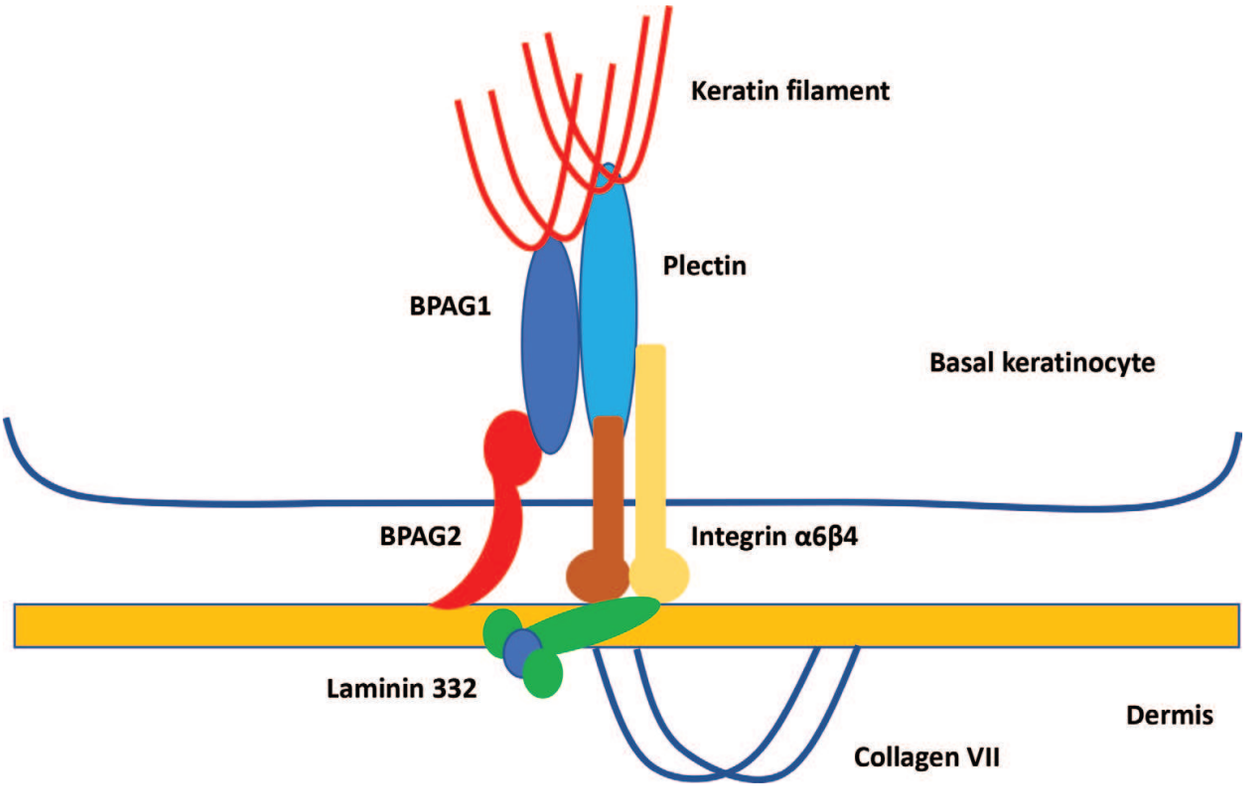

Figure 3. The structure of hemidesmosome. BPAG: Bullous pemphigoid antigen.

extracellular matrix (ECMs), resulting in increased motility. Forced expression of keratin 5 and 14 pairs in the keratin-null keratinocytes, the basal keratinocyte pair of keratins, caused suppressed migration ability. Enhanced migration occurs also in keratinocytes null for epiplakin, plectin, plakoglobin, plakophilin or keratin K6 (K6a/K6b). Loss of keratin K6, plectin or plakoglobin causes activation of Src family kinase, and F-actin reorganization. Src kinase regulates leading edge protrusion though Rac and Cdc42 signaling pathway, which also stimulate to form invadopodia, actin-rich cellular protrusion which works in ECM degradation and cancer invasion and metastasis. Src also directly induces epithelial and mesenchymal transition. Src directly interacts with keratin intermediate filaments in a K6-dependent manner [6]. K6(K6a/K6b) null keratinocytes show enhanced migration, however, K6 is induced in wound healing process where keratinocyte migration is needed. Thus, expression of keratins appears inhibitory to cell migration, which is opposite to expression of vimentin, the type III IF, resulting in enhanced migration and invasion of cancer cells.

3. Regulation of expression of inflammatory keratins

Epidermis covers the outermost surface of human skin. It should withstand the environmental stimuli, such as infection, allergens, and mechanical and chemical insults. Epidermis changes its cytoskeletal keratin expression in inflammatory conditions. Normal healthy interfollicular

epidermis expresses keratin K1 and K10 in suprabasal layers, and keratin K5 and K14 in basal layer, while in inflammatory skin conditions, such as psoriasis and atopic dermatitis, expression of keratin K1 and K10 are suppressed and expression of inflammatory keratins, such as keratin K6, K16 and K17 are induced.

Dr. Blumenberg and our group have investigated on the mechanism of induction of these inflammatory keratins. Epidermal growth factor (EGF) induced expression of inflammation and proliferation-related keratins K6 and its counterpart K16 at transcriptional level [7–9]. Interferon (IFN) γ induced keratin K17 promoter activity through transcription factor STAT1 [10, 11]. Tumor necrosis factor (TNF) α induced K6 promoter activity through NFκB and C/EBPβ [12]. Interleukin (IL)-1 induced K6 through C/EBPβ, which binding site clearly distinct from EGF response element [13]. IFNγ also induced keratin K6 through STAT1 signaling pathway [14]. These results indicate that inflammatory cytokines and growth factors induce inflammatory and proliferation-related keratins, at the transcriptional level, which may result in keratinocyte activation in inflammatory skin diseases, such as atopic dermatitis and psoriasis.

Mechanical stimuli are one of important external stimuli, which epidermal keratinocytes respond in daily life. Scratching causes mechanical stretch as well as barrier disruption, and use of tissue expander results in mechanical stretch of epidermal keratinocytes. Pregnant women experiences expansion of abdominal skin caused by growing fetus, especially in third trimester. These mechanical stimuli should influence epidermal keratinocytes through cell–cell junction and cell-ECM junction, such as desmosomes and hemidesmosomes. We have utilized stretchable silicon chamber and examined the effect of mechanical stretch on epidermal keratinocytes. Mechanical stretch induced phosphorylation of EGFR, ERK1/2, and inflammation-related keratin K6, and suppressed differentiation-related keratin K10 [15, 16].

4. Mutation in keratin gene causes various skin diseases and predisposition to internal diseases

Keratin gene mutations causes various diseases, called “keratinopathies” or “keratin disorders”. Mutations in epidermal keratins causes skin diseases, such as congenital ichthyosis, congenital bullous disease, and pachyonychia congenita. Mutations in corneal keratins, K3 and K12, cause corneal dystrophy, and mutations in oral keratins, K4/13, cause white sponge nevus in oral mucosa. These causative mutations occur mostly in the conserved region of keratin genes, that is, the beginning/end portion of rod domain, which often affects normal filament assembly, and causes aggregation of keratin protein in the cytoplasm. Mutant keratin affects normal keratin (dominant negative effect), which often results in dominantly inherited congenital diseases. On the other hand, mutation in simple epithelial keratins, such as K8/18 and K19, is found in less conserved regions, which constitutes the risk factors for liver disease and inflammatory bowel diseases.

Mutation in keratin K1 or K10, the differentiation-related epidermal keratins, expressed in the suprabasal layers of epidermis, causes epidermolytic ichthyosis, previously called bullous

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congenital ichthyosiform erythroderma. The affected child shows erythroderma with bulla formation and later develops ichthyotic skin. The characteristic histological feature is epidermolytic hyperkeratosis, in which hyperkeratosis and coarse keratohyalin granules in degenerated, vacuolar cytoplasm of the granular layer keratinocytes are prominent. The same mutation, when occurred during embryonic development, causes epidermolytic epidermal nevus, aligned in the lines if blaschko, showing similar histological changes in affected skin. Keratin 9 is expressed specifically in the skin of palms and soles. When similar mutations occur in keratin 9, similar histological change, epidermolytic hyperkeratosis, is seen in the epidermis of palms and soles, resulting in Vörner type palmoplantar keratoderma. In these conditions, similar keratin aggregation is observed in the cytoplasm of affected keratinocytes [2, 17].

Keratin 5 and 14 are expressed in pair in the basal layer keratinocytes. Mutation in keratin 5 or 14 causes epidermolysis bullosa simplex, one of congenital bullous disorder. Disruption of keratin filament network in basal keratinocytes with keratin mutation results in collapse of basal keratinocytes, leading to bulla formation at the bottom of the epidermis. Epidermolysis bullosa simplex is one of congenital bullous disease, caused by mutation in basal cell keratin, K5 and K14. Mutated keratin causes fragility in basal keratinocytes where keratin K5 and K14 are expressed, results in intraepidermal bulla formation. Existence of keratin mutations or the reduced expression of keratins cause reduction of desmosome expression and cytoskeletal linker protein expression, resulting in increased motility of keratinocytes. The reduced expression of desmosomes, the junction proteins, may be another mechanism of tissue fragility in EBS patients. Mutations in K5 or K14 in EBS also cause alteration in cellular response to external stress. Keratinocytes with K5 or K14 mutation show increased activation of stress-activated protein kinase (SAPK) signaling against external stresses, as well as constitutive activation of extracellular-signal-regulated kinases (ERKs) [1, 2].

Pigmentary disorder, called Dowling-Degos disease (DDD), has been disclosed to be due to mutation in keratins K5 or K14, and Galli-Galli disease (GGD) due to mutation in keratin K5. DDD patients classically show small pigmented macules and reticulated pigmentation in the large folds and flexure surface. Some patients show pigmentation on the face, and also comedo-like papules and pitted scarring are seen. GGD patients show similar clinical features, with distinct histological changes, including acantholysis. Patients with EBS with mottled pigmentation show similar pigmentary changes with vesicle formation. Mutations in keratin K5 have been reported to cause EBS since the 1990s; there is a genotype–phenotype correlation between keratin mutation and the type of EBS. The most severe form, Dowling-Meara type, is caused by mutation in the highly conserved region on the either side of the helix boundary area of rod domain, while the milder type of EBS, Koebner type, and Weber-Cockayne type are caused by mutations occurred throughout the rod domain. There is a subtype of EBS with mottled pigmentation caused by mostly specific mutation p.Pro25Leu, in the head domain of keratin K5. Mutations in K5 of DDD and DDG are also in the head domain of K5, which are nonsense mutation or frameshift mutation, resulting in premature stop codons, leading to haploinsufficiency of K5 rather than dominant negative effect. These cases demonstrate that keratin K5 is important in melanosome transportation. Melanosomes, one of cell organelles containing melanin, are produced in melanocytes and transferred to keratinocytes where

melanosomes distribute in the cytoplasm. Mutation in K5 results in melanosome transfer and the distribution of melanosomes in keratinocytes, leading to altered pigmentation in skin. Thus, keratins may also contribute in organelle transfer in keratinocytes [1].

Keratin K6, K16, and K17 are expressed in follicular epithelium, oral mucosa, palms and soles and nails. They are also induced in inflammatory skin diseases in interfollicular epidermis. Mutation in keratin K6, K16 or K17 causes pachyonychia congenita, showing thick and deforming nails and hyperkeratotic palms and soles, with or without steatocystoma multiplex. Pachyonychia congenita (PC)-1, is a form of PC presenting with nail defects, palmoplantar hyperkeratosis, follicular hyperkeratosis, and oral leukokeratosis. PC-2 lacks oral involvement, but has multiple folliculosebaceous cysts and natal teeth. Kratin 6 consists of three isoforms, K6A, K6B and K6C. K6A is the most abundant isoform, which makes pair with K16, and the mutation in K6A, as well as K16 leads to PC-1. K6B is a counterpart of K17, and mutation in K6B or K17 leads to PC-2 [2, 17]. These keratins, K6, K16 and K17 are induced by several cytokines and growth factors, such as EGF, TNF and IFNγ, or by mechanical stress or UV. The attempt to suppress the expression of mutated keratins has been done by several researchers to treat PC patients. Small interfering RNA for mutant K6a has been tried to treat PC patients, demonstrating feasible therapeutic strategy for keratin disorders [18]. RNA interference, however, harbors potential risk for off-target effects, which should be effectively avoided. Recently, K16 has been disclosed to be involved in the induction of danger-associated molecular patterns (DAMPs)/alarmins and skin barrier genes [19], and the regulator of nuclear factor erythroid-derived 2 related factor 2 (NRF2). In PC lesional epidermis, NRF2 protein expression is elevated, but the activation of NRF2 is suppressed, similar to Krt16−/− mice which present PC-like skin lesions. Reduction in active NRF2 results in reduced glutathione (GSH) levels, indicating increased oxidative stress. Inhibitor of GSH synthesis has been shown to induce PPK in mice, which imply that reduced NRF2 activity in Krt16−/− mice caused PPK through reduction in GSH levels and increased oxidative stress. Topical application of sulforaphane, an activator of NRF2, rescued PPK in Krt16−/− mice, as well as increasing the levels of NRF2, and pNRF2, indicating the possibility of treating PPK with small molecule targeted drugs pharmacologically activating NRF2 [20].

Mutations in K8 or K18, simple epithelial keratins, have been shown to be the risk factor for some patients with inflammatory bowel diseases or liver disease. Mutation in cytoskeletal keratins causes reduced resilience in epithelia of digestive tract which is always under mechanical stress and peristaltic movement, resulting in cellular damage. Mutations in keratin in liver cause reduced tolerance to toxins, such as alcohol and drugs, thus predispose patients to liver damage at situations of cell stress. Keratin K8 undergoes hyperphosphorylation, acting as phosphate sponge to absorb various phosphorylated proteins, such as SAPK and ERKs, and reduce inflammation and apoptosis [2, 17].

5. Keratins and inflammatory diseases and cancer

Keratin filaments regulate inflammatory processes. Wild-type keratin K8 has been reported to be a negative regulator of inflammation by suppressing TLR signaling through inhibiting

NFκB activation [21]. Keratin 8 also protects colonic epithelium from inflammation, and cancer progression [22, 23] Wild-type keratins suppress TSLP production. Normal human epidermal keratinocytes do not produce TSLP in culture, while keratin null keratinocytes produce copious amount of TSLP [24]. They showed that defects in keratins caused activation of MEK1/2 and ERK1/2, resulting in TSLP production independent on barrier disruption. Keratin 17 expression promotes inflammation towards Th1- and Th17-type immune reactions, the characteristic inflammation in psoriasis, and the absence of K17 attenuates inflammation and tumorigenesis [25]. C-terminus of K6 has anti-microbial properties [26]. Mice with K1 expression in pancreas βcells develop diabetes with decreased insulin secreting vesicles. K17 binds to 14-3-3σ and TRADD, and loss of K17 results in altered inflammatory cytokine production, impaired wound healing and impaired hair follicle cycling [2]. K14 also directly binds to TRADD, which influences the signaling pathway through TNFR [27]. K16 knockout mice show increased activity of danger signals, described as above. Another report showed that the amount of keratin protein itself is important to protect cells against mechanical stress [28].

Keratins are also involved in cancer proliferation and invasion. Keratin 19 fragment (CYFRA) has been used in clinics for tumor marker, especially to detect non-small cell lung cancer. Not only as a tumor marker, K19 promotes tumor cell invasion in hepatocellular carcinoma, probably by formation of invadopodia [29]. Cancer cell with K19 expression also shows increased resistance to chemotherapy [1].

6. Conclusion

Keratins are cytoskeletal proteins, however, not only that, keratins have various roles in physiology and pathophysiology of human organs, and involved in proliferation, motility and invasion of the cells, and inflammation of tissues. Their complexed behavior would be further elucidated in future, and many more novel findings would help exploring the target of future therapy of inherited cutaneous diseases, cancer and inflammatory disorders.

Conflict of interest

None.

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