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REVIEW ARTICLE

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Keratins and epidermolysis bullosa simplex

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Keratin intermediate filaments play an important role in maintaining the integrity of the skin structure. Understanding the importance of this subject is possible with the investigation of keratin defects in epidermolysis bullosa simplex (EBS). Nowadays, in addition to clinical criteria, new molecular diagnostic methods, such as next generation sequencing, can help to distinguish the subgroups of EBS more precisely. Because the most important and most commonly occurring molecular defects in these patients are the defects of keratins 5 and 14 (KRT5 and KRT14), comprehending the nature structure of these proteins and their involved processes can be very effective in understanding the pathophysiology of this disease and providing new and effective therapeutic platforms to treat it. Here, we summarized the various aspects of the presence of KRT5 and KRT14 in the epidermis, their relation to the incidence and severity of EBS phenotypes, and the processes with which these proteins can affect them.

KEYWORDS
epidermolysis bullosa simplex (EBS), keratin, molecular aspects

1 | MOLECULAR ASPECTS OF KERATIN

The epidermis (superficial skin layer) has many important physiological roles, including creation of a physical barrier against the influence of external factors, setting a body temperature, defensive performance, protection of the body and internal organs against the destructive effects of sunlight (Segre, 2006). In the human body, the formation of the epidermis from the primary ectoderm begins in the first 4 months of pregnancy. Then, in 28-day periods, it is recreated by very regular processes. In this period, keratinocytes, which are the majority of epidermal cells, gradually differentiate into four consecutive cell layers. These layers include a layer with proliferation power (called stratum basale) and three differentiated cellular layers (called stratum spinosum, stratum granulosum, and stratum corneum) (Segre, 2006).

Given that the epidermis is the outer layer of the skin and is constantly exposed to external (environmental) factors, the epidermis should withstand various stresses, such as mechanical erosion and temperature change (Pekny & Lane, 2007). All over the epithelial cell cytoplasm, a uniform spatial network of filaments is created by keratins. In fact, keratin, by attaching to a cell membrane at the site of

desmosome junction and hemidesmosome junction to the nuclear membrane, plays an important role in maintaining the integrity of the epidermis. Hence, the ability to withstand environmental tensions and stresses is due to keratinocytes (keratin producing cells; Godsel, Hobbs, & Green, 2008).

Keratin is a member of the protein family of intermediate filaments and is the most abundant protein in the epithelial cells cytoplasm (Omary, Coulombe, & McLean, 2004). Structurally, keratins have a central rod-shaped alpha helix domain and two nonhelix domains on both sides (tail and head). This structure is common among all types of keratins. At the beginning and the end of a central rod-shaped region, there are two strongly conserved and unchanged amino acid sequences, which are called initial and terminal helices. In the formation of helix–helix heterodimer structures in keratin molecules, these initial and terminal structures play a very important role (Omary et al., 2004).

Keratins are divided into two categories: type I (acidic) and type II (alkaline). They are organized in two gene clusters in chromosomal positions 17q21.2 and 12q13.3, respectively (Omary et al., 2004). The diversity observed in living cells is due to the multiplicity of keratin genes as well as the plurality of polymeric connections of keratins type I and II (Hatzfeld & Franke, 1985). The differentiation of keratinocytes is determined by the expression pattern of the keratin gene (highly regulated; Lane & McLean, 2004). The keratinocytes located on stratum basal mainly express keratins 5 and 14 (KRT5 and KRT14; Langbein et al., 2005; Nelson & Sun, 1983). KRT2 is expressed on the higher epidermis suprabasal layers (Collin, Moll, Kubicka, Ouhayoun, & Franke, 1992). Among the keratins, some are expressed in a specific anatomical region only. For example, KRT9 is expressed on the skin of the hand palm and foot sole (Langbein, Heid, Moll, & Franke, 1993) and KRT6b and KRT17 are expressed in follicular epithelium cells (Covello et al., 1998; Smith et al., 1998; Wojcik, Longley, & Roop, 2001). In addition to specific anatomical expression, some types of keratin are expressed in terms of specific conditions. For example, KRT6a and KRT16 are expressed at the time of wound healing (Rosenberg, RayChaudhury, Shows, Le Beau, & Fuchs, 1988; Wojcik, Bundman, & Roop, 2000). Keratins play an important role in maintaining cellular structure and differentiated or specialized normal cellular function in the epithelial layer (Moll, Divo, & Langbein, 2008). These proteins are involved in some of the nonstructural regulatory processes including protein synthesis (Kim, Wong, & Coulombe, 2006), cell migration (Tao, Berno, Cox, & Frazer, 2007), and apoptosis (Tong & Coulombe, 2006).

2 | EPIDERMOLYSIS BULLOSA SIMPLEX AND KERATINS

Epidermolysis bullosa simplex (EBS) is one of the most common genetic bullous skin diseases. It is characterized by the separation of the skin at the basal keratinocytes region after trauma and blister formation (Fine et al., 2008). It is estimated that the incidence of this disease is about one in every 25,000–50,000 people (Pfendner, Uitto, & Fine, 2001).

It is worth noting that in Western countries (because of the low level of consanguineous marriages), most people with EBS have an autosomal dominant inheritance pattern. However, in countries with more consanguineous marriages, such as Middle Eastern countries, the autosomal recessive form is more common (Ciubotaru et al., 2003; McKenna, Walsh, & Bingham, 1992; Sa'd et al., 2006). Based on the region of blister formation in the epidermis, epidermolysis bullosa disease is classified into four groups: intraepidermal (EBS/epidermolytic), intralamina lucida (junctional EB), sublamina densa (dystrophic EB), and Kindler syndrome (Intong & Murrell, 2012). EBS is known as a heterogeneous group, which is divided into four most common subtypes (Pfendner et al., 2016): localized EBS (also known as Weber–Cockayne type), generalized intermediate EBS (also known as Koebner type), EBS with mottled pigmentation, and generalized severe EBS (also known as Dowling–Meara type). EBS based on site of cleavage is divided into two groups: suprabasal EBS and basal EBS, which are classified in Table 1. KRT5 and KRT14 gene mutations are responsible for approximately 75% of cases with EBS (Bolling, Lemmink, Jansen, & Jonkman, 2011; Pfendner et al., 2016). Heterozygous missense mutations in KRT5 and KRT14 genes are the most common cause of disease in people with EBS (Bolling et al., 2011; Lane & McLean, 2004). However, as mentioned above, in Western societies, because of low prevalence of consanguineous marriages, a large number of patients with EBS have an autosomal dominant inheritance pattern. However, with an increase in the prevalence of consanguineous marriages, more recessive cases are seen. For example, in the Middle East, about 30% of patients have recessive mutations in KRT14 (Ciubotaru et al., 2003; Sa'd et al., 2006). The phenotypes produced by KRT5 and KRT14 genes mutations are classified in Table 2 with their clinical criteria.

Most of the KRT5 and KRT14 mutations affect these filaments in the central alpha helix region. Disturbance in this part render these keratin molecules incapable of tolerating even low levels of mechanical pressure. Subsequently, the basal cellular layer is exposed to cytolysis (Uitto, Richard, & McGrath, 2007).

The phenotype–genotype analysis of patients has shown that the relationship between the mutations affect the preserved initial and the terminal points of the central rod and the creation of a more severe phenotype (EBS Dowling–Meara [EBS-DM]). While mutations affecting the less-protected areas of keratin molecules are associated with a milder phenotype (localized EBS) (Uitto & Richard, 2005; Uitto & Richard, 2004; Liovic et al., 2001; however, this does not happen all the times) (Ciubotaru et al., 2003; Sa'd et al., 2006). It should be noted that in addition to the spatial location of the mutation, the nature of the replaced amino acid also affects the severity of the disease (Murrell, Trisnowati, Miyakis, & Paller, 2011; Sørensen et al., 1999).

To treat EBS, the investigation of molecular pathology plays a crucial role. Because most EBS-induced mutations have a dominant negative effect, the introduction of a natural allele to cell may not affect the treatment patients with EBS. A more effective way to treat

TABLE 1 Classification of EBS based on cleavage site

Site of cleavage	Gene	Protein	Types of EBS	OMIM	Mode of Inheritance	Reference
Suprabasal EBS	*DSP*	Desmoplakin	Lethal Acantholytic EB	609638	AR	(Bolling, Veenstra et al., 2010; Jonkman et al., 2005)
	JUP	Plakoglobin	Lethal Congenital EB		AR	(Pigors et al., 2011)
	PKP1	Plakophilin-1	Ectodermal Dysplasia–Skin Fragility syndrome	604536	AR	(McGrath et al., 1997)
Basal EBS	*KRT5*	Keratin 5	Dowling–Meara	131760	AD	(Lane et al., 1992; Pfendner, Sadowski, & Uitto, 2005a; Rugg et al., 1999)
			Generalized intermediate EBS (formerly, Koebner type)	131900	AD	(Dong, Ryynänen & Uitto, 1993; Pfendner, Sadowski, & Uitto, 2005b; Stephens et al., 1995)
			Localized EBS (formerly, Weber-Cockayne)	131800	AD	(Y. M. Chan et al., 1994; Y. M. Chan, Yu, Fine, & Fuchs, 1993; Yasukawa, Sawamura, McMillan, Nakamura, & Shimizu, 2002)
			Dowling-Degos disease	179850	AD	(Betz et al., 2006; Crovato, Nazzari, & Rebora, 1983)
			EBS with migratory circinate erythema	609352		(Gu et al., 2003)
			EBS with mottled pigmentation	131960	AD	(Uttam et al., 1996)
			Autosomal recessive EBS	601001	AR	(Yasukawa et al., 2002)
	KRT14	Keratin 14	Dowling–Meara	131760	AD	(Coulombe et al., 1991; Hut et al., 2000; Pfendner et al., 2005a)
			Generalized intermediate EBS (formerly, Koebner type)	131900	AD	(Bonifas, Rothman, & Epstein, 1991; Humphries et al., 1993; Pfendner et al., 2005b)
			Localized EBS (formerly, Weber-Cockayne)	131800	AD	(Chen, Bonlfas, Matsumura, Blumenfeld & Epstein, 1993)
			Autosomal recessive EBS	601001	AR	(Y. M. Chan et al., 1994; Hovnanian et al., 1993; Rugg et al., 1994)
	ITGB4	Integrin β4	EBS junctional is with pyloric atresia	226730	AR	(Chavanas et al., 1999; Vidal et al., 1995)
			localized EBS (formerly, Weber-Cockayne)	131800	AD	(Jonkman, Pas, Nijenhuis, Kloosterhuis, & Steege, 2002)
	PLEC1	Plectin	EBS with muscular dystrophy	226670	AR	(Bolling, Pas et al., 2010; Smith et al., 1996)
			EBS Ogna type	131950	AD	(Koss-Harnes et al., 2002)
			Lethal EBS	612138	AR	(Bonduelle et al., 2003)
			EBS with pyloric atresia			(Nakamura et al., 2005)
	DST	Dystonin (BPAG1-e) epithelial isoform of bullous pemphigoid antigen 1	EBS, autosomal recessive with neurologic symptoms	615425	AR	(Groves et al., 2010)
	TGM5	Transglutaminase 5	Acral peeling skin syndrome	609796	AR	(Cassidy et al., 2005; Kharfi et al., 2009)
	EXPH5	Exophilin 5	EBS, nonspecific, autosomal recessive	615028	AR	(McGrath et al., 2012)
	KLHL24	Kelchlike family 24	Epidermolysis bullosa simplex, generalized, with scarring and hair loss	617294	AD	(He et al., 2016; Lin et al., 2016)

Note. AD: autosomal dominant; AR: autosomal recessive; EBS: epidermolysis bullosa simplex; OMIM: Online Mendelian Inheritance in Man.

TABLE 2 The phenotypes created by KRT5 and KRT14 genes mutations

Types of EBS	Clinical features	Reference
Dowling–Meara type (generalized severe)	• Common mutation: heterozygous missense K14 mutation R125C which affects the helix initiation motif in the helix 1A • The most severe form • Onset age: commonly at birth • Pervasive blistering occurring from birth • Blisters occur in herpetiform clusters on the trunk and proximal extremities • Healing of blisters with minor scarring • Nails dystrophy • Milia • Progressive hyperkeratosis of the palms and soles • Hypopigmentation and hyperpigmentation • Neonatal or infant death due to high severe blistering • Mucosal involvement: frequently	(Anton-Lamprecht & Schnyder, 1982; Ishida-Yamamoto et al., 1991; McGrath et al., 1992; Pfendner et al., 2016; Smith, 2003; Smith, Irwin Mclean, & Morley, 2004)
EBS, Koebner type (generalized intermediate)	• Onset age: at Birth or early infancy • Severity of Involvement: Intermediate EBS-localized and EBS-generalized severe • Mucosal and teeth involvement: may be mildly involved • Hyperkeratosis of the palms and soles occur sometimes • Hypopigmentation and hyperpigmentation, milia maybe arise	(Pfendner et al., 2016)
Localized EBS (previously EBS, Weber-Cockayne)	• The mildest form • Onset age: rarely at birth, usually at Infancy with 12–18 months age, occasionally in adolescence or early adulthood • Hyperkeratosis of the palms and soles occur sometimes • Blisters Typically restricted to hands and feet • Mucosal involvement: Infrequent • There is no trace of hypopigmentation and hyperpigmentation	(Y. M. Chan et al., 1993; Pfendner et al., 2016)
Dowling-Degos disease	• Blistering is not observed • Acantholysis is often seen • Consequences of abnormality in transport of melanosome and growth of epithelia are: • Reticulate hyperpigmentation of the flexures • Comedolike lesions on the neck • Pitted perioral acneiform scars	(Betz et al., 2006; Jones & Grice, 1978; Sprecher et al., 2007)
EBS with migratory circinate erythema	• Common mutation: a frameshift mutation (c.1649delG) disturbing the construction of tail domain of keratin 5 • Vesicles incidence on the background of a migratory circinate erythema • Intraepidermal blister formation • The lesions often heal with no scarring and brown pigmentation(brown postinflammatory hyperpigmentation)	(Castiglia et al., 2014; Choi & Kim, 2016; Gu et al., 2003)
EBS with mottled pigmentation	• Common mutation: a missense mutation (p.P24L) affecting KRT5 head domain • Skin blistering • Reticulate skin pigmentation • Keratoderma • Nail dystrophy • Other mutations in KRT5 and KRT14 has been reported that create same phenotype	(Browning & Mohr, 2012; Harel, Bergman, Indelman, & Sprecher, 2006; Irvine et al., 2001; Uttam et al., 1996)

(Continues)

TABLE 2 (Continued)

Types of EBS	Clinical features	Reference
Autosomal recessive EBS	• Cause: missense or nonsense mutations in *KRT14* resulting in loss of function rather than a dominant-negative effect • Muscular dystrophy • Growth retardation • Anemia	(Hovnanian et al., 1993; Sa'd et al., 2006)

Note. EBS: epidermolysis bullosa simplex; KRT5: keratin 5; KRT14: keratin 14.

EBS is to remove mutated keratin molecules (Smith et al., 2004; Cao, Longley, Wang, & Roop, 2001).

The important point is that as the patient's age increases, upon increasing or compensating the expression of keratin genes with less expression in the basal cell layer (such as KRT15) and reducing the expression of mutated keratin genes, the patient phenotype is relatively improves (Jonkman et al., 1996). The genetic background of people and their ethnicity is also important in determining the genotype–phenotype communicative aspects in different families and populations (Sa'd et al., 2006). Revertant mosaicism has also been reported in one case with EBS-DM and another patient with Recessive EBS (revertant Mosaicism of Keratin 14; Schuilenga-Hut et al., 2002; Smith et al., 2004). It should not be forgotten that the effect of nongenetic factors should not be ignored. These nongenetic factors may affect the effectiveness and incidence of sequence changes (genetic changes), for example, the relationship manifestation of transient EBS-like phenotype after treatment by bexarotene in the presence of a silent polymorphism in KRT5 gene (Trufant et al., 2010).

3 | OTHER REGULATORY EFFECTS OF KERATIN IN EBS

Structural fractures that occur in basal keratinocytes due to keratin gene mutations are the cause of skin blistering in people with EBS (Ma, Yamada, Wirtz, & Coulombe, 2001). However, phenotypic manifestations are not limited to the above-mentioned mechanism. Other mechanisms can be related to the disease phenotype. Some mutations in the keratin gene affect the dynamism of cellular skeletons or interfere with changes occurring after translation in natural keratin (Coulombe & Omary, 2002; Werner et al., 2004).

Increase in apoptosis activity was also observed in these patients. There is a strong possibilty that it is due to keratin aggregations and upregulation of inflammatory responses in the pathogenesis of EBS (Lu et al., 2007; Yoneda et al., 2004). One of the characteristics of EBS-DM is that the mutated keratin proteins that are badly polymerized are accumulated in the cytoplasm. This affects cellular and tissue pathophysiology. Therefore, the formation of a tissue and cellular stress to respond to these cytoplasmic aggregations is not unlikely (D'Alessandro, Russell, Morley, Davies, & Lane, 2002; Löffek et al., 2010).

A study on the gene expression analysis in a specific cell category of EBS-DM containing mutation in KRT14 gene indicated the upregulation of the genes involved in controlling the development, apoptosis, migration, epidermis and wound healing as a molecular result of mutation in KRT14 (Wagner, Hintner, Bauer, & Onder, 2012).

A study on mouse transgenic models (Coulombe & Lee, 2012) presents several new functions for the keratin proteins existing in the skin epithelium, including the regulation of cell and tissue growth in the epidermis and hair follicles (Reichelt & Magin, 2002; Tong & Coulombe, 2006) and increasing keratinocytes proliferation (Coulombe & Lee, 2012; DePianto, Kerns, Dlugosz, & Coulombe, 2010), which may be related to the incidence of EBS. The expression of preinflammatory and/or mitogenic cytokines or chemokines increases the proliferation of keratinocytes (DePianto et al., 2010).

4 | IMMUNOLOGICAL PERSPECTIVE OF KERATINS IN EBS

Inflammation is one of the most important factors for the incidence of pathologic complications of EBS. The mutation occurring in K5 and K14, followed by changes in the structure of extracellular matrix filaments, can increase the patient's sensitivity to mechanical stresses. Studies on $k5^{-/-}$ rats revealed that in the absence of keratin filaments, the epidermis is completely separated from the derma, resulting in severe symptoms (Cao et al., 2001; Peters, Kirfel, Büssow, Vidal & Magin, 2001).

In addition to mechanical damages, which are the main cause of EBS symptoms in patients with mutated keratin, other pathological mechanisms can also play a role in promoting it. They include preinflammatory cytokines and signaling pathways associated with them (Lu et al., 2007; Yoneda et al., 2004).

The tumor necrosis factor (TNF) performs its function through binding to its receptor at the target cells surface including TNFR1 and TNFR2. TNF binding to TNFR1 leads to the transfer of signals through its cytoplasmic death domains via activating the proteins adaptor, which converts procaspase 8 to active caspase 8. After this, by activating proteases, the process of apoptosis occurs. In a study, Yoneda et al. (2004) showed that TNF could lead to the death of HaCaT keratinocyte cell line that was transiently transfected with mutated K14 (K14Arg125Cys). This study indicated that these cells release TNFα, which can lead to cell death via activating the TNFα receptor in autocrine/paracrine pathways (Russell, Andrews, James, & Lane, 2004).

IL1β is another preinflammatory cytokine that can play an important role in EBS disease. This cytokine activates keratinocytes.

In basal keratinocytes, Interleukin-1β is present in the cytoplasm in the precursor form. After damage, it is processed and released. Like TNF, as paracrine/autocrine, it leads to the change of gene expression and ultimately the proliferation and migration of cells (Freedberg, Tomic-Canic, Komine, & Blumenberg, 2001).

One of the signaling pathways involved in EBS is the activation of ERK and Akt due to mechanical stresses. The findings indicate that the activation of this signaling pathway causes resistance to apoptosis in keratinocyte cells with mutated keratin (Russell, Ross, & Lane, 2010).

In addition, the activation of relevant transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), could provide the chemokines (i.e., CCL20, CCL19, and CCL2) which are needed for a variety of biological processes, such as recruitment, migration, and maturation of langerhans cells (Roth, Reuter, Wohlenberg, Bruckner-Tuderman, & Magin, 2009). Langerhans cell, as epithelium resident cells, present dendritic cells that can be produced by of cytokines, and the expression of different molecules on their surface plays an important role in stimulating or inhibiting the immune system (Banchereau et al., 2012; Seneschal, Clark, Gehad, Baecher-Allan, & Kupper, 2012; Stoitzner, 2010). Various studies have shown that langerhans cells can play a role in facilitating DNA destruction in epithelial cells and squamous cell carcinoma (SCC) incidence. SCC is one of the main causes of death in patients with EB (Montaudié, Chiaverini, Sbidian, Charlesworth & Lacour, 2016).

5 | CONCLUSION

EBS is known as a heterogeneous group of genetic skin disorders, which have many genetic reasons. Among these, the role of Keratins (KRT5 and KRT14) is more powerful. KRT5 and KRT14 are the major keratins, which are expressed in the basal epidermis. These proteins, according to their own structure and as a member of the protein family of intermediate filaments, play an important role in conserving the integrity of the skin structure. To help patients with EBS and move on to a practical treatment in the future for these patients, the exact recognition of these proteins and the mechanisms involved is imperative.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interests.

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