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Review

Lessons from disorders of epidermal differentiation-associated keratins

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Summary. A number of diseases have been associated with mutations in genes encoding keratin intermediate filaments. Several of these disorders have skin manifestations, in which histological changes highlight the role of various different keratins in epidermal differentiation. For example, mutations in either K1 or K10 (the major keratin pair expressed in differentiated keratinocytes) usually lead to clumped keratin filaments and cytolysis. Furthermore, the precise nature of the mutation has direct implications for disease phenotype. Specifically, mutations in the H1 and alpha-helical rod domains of K1/K10 result in bullous congenital ichthyosiform erythroderma, underscoring the critical role for this keratin filament domain in maintaining cellular integrity. However, a lysine to isoleucine substitution in the V1 domain of K1 underlies a form of palmoplantar keratoderma, which has different cell biological implications. Keratins are cross-linked into the cornified cell envelopes through this particular lysine residue and the consequences of the mutation lead to changes in keratin-desmosome association and cornified cell morphology, suggesting a role for this keratin sub-domain in cornified cell envelope formation. Recently, to extend genotype-phenotype correlation, a frameshift mutation in the V2 region of the K1 tail domain was identified in ichthyosis hystrix (Curth-Macklin type), in which keratin filaments show a characteristic shell-like structure and fail to form proper bundles. In this case, the association of desmosomes with loricrin was also altered, implicating this keratin domain in organizing the intracellular distribution of loricrin during cornification. Collectively, these mutations in K1/K10 provide a fascinating insight into both normal and abnormal processes of epidermal differentiation.

Key words: Ichthyosis Hystrix type Curth-Macklin, Inherited skin diseases, Keratin, Keratinocytes, Palmoplantar keratoderma

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Introduction

Keratins are a major member of the intermediate filament family of proteins. Clues to the function of several keratins have been derived from a growing number of diseases associated with mutations in the corresponding keratin genes (Table 1) (Corden and McLean, 1996; Irvine and McLean, 1999). These findings have provided insight into our understanding of the functional significance of keratins within keratinocytes.

Several distinct skin diseases are caused by a mutation of epidermal differentiation-associated keratins, K1 and K10. This review will focus on 1) the properties of keratins; 2) specific diseases of K1/K10 with special reference to ichthyosis hystrix type Curth-Macklin, a recently identified disease of K1; and 3) the implications of keratin mutations for our understanding of keratinocyte biology.

Keratins

Keratins are organized as a central alpha-helical rod domain flanked by nonhelical, variable end domains (Fig. 1) (for reviews see Fuchs et al., 1994; Steinert et al., 1994). The central rod domain is composed of four alpha-helical subdomains interrupted by three short nonhelical spacer segments. The central alpha-helical rod domains, particularly their highly conserved amino end (helix initiation sequence) and carboxy end (helix termination sequence), are critical for filament assembly, but non-helical spacer segments seem to be less important. The non-helical amino and carboxy end domains are highly variable and may provide cell type-specific properties.

Keratins are obligatory heteropolymers of type I and type II keratin peptides. Keratin molecules are thought to be self-assembled initially as a heterodimer of a specific pair of type I and type II keratins, aligned in parallel and intertwined in a coiled-coil rod. However, it remains to be determined how these dimers actually align and form the characteristic 10 nm-sized intermediate filaments and finally the three-dimensional ordered networks that

extend to form the peri-nuclear region to the (hemi) desmosomes. In the skin, the epidermal keratinocytes express four major keratins, two type II keratins (K1 and K5) and two type I keratins (K10 and K14). K5 and K14 are the main keratin pair expressed in the basal cells. When the cells commit to differentiate and move up to the suprabasal cell layers, synthesis of this pair is down-regulated with a concomitant expression of a new keratin pair, K1 and K10.

Biological functions of keratins have been studied in various experimental systems. Functions of keratins in a more complex system, *in vivo*, have been best demonstrated by "experiments in nature", human keratin disorders. There are strong correlations between the affected sites or organs and the expression patterns of mutant keratins (Table 1). For example, when either K5 or K14 are mutated, skin blisters occur upon subtle mechanical stress within the basal cell layer, manifesting themselves as the skin blistering disease, epidermolysis bullosa simplex. This suggests that a primary function of keratins is to provide mechanical integrity to epidermal cells. In the following section, we will review a wide range of clinical and histological presentations resulting from mutations in K1 and K10, and what we have learned from them.

Disorders of epidermal differentiation-associated keratins, K1/K10

Bullous congenital ichthyosifom erythroderma (BCIE) and its variants

BCIE is an autosomal dominant disorder characterized by skin blistering and erythroderma in neonates and infancy, followed by persistent generalized hyperkeratosis. Its characteristic histopathological feature is epidermolytic hyperkeratosis, showing marked hyperkeratosis, hypergranulosis, vacuolization of the spinous and granular cells, and coarse cytoplasmic granules. Immunoelectron microscopy examination shows some of these granules to actually comprise clumped keratin filaments composed of K1 and K10 (Ishida-Yamamoto et al., 1992). The keratin clumping occurs only in the cells that express K1 and K10; thus it is seen from the suprabasal cells in the epidermis. These cytoskeletal defects impair cellular mechanical strength and cell integrity, which is manifested by skin blistering.

BCIE is caused by a gene mutation in one allele of either K1 or K10 (for a review, see Corden and McLean, 1996. For mutations found more recently, see Arin et al., 1999a,b; Yang et al., 1999a,b; McLean et al., 1999; Cserhalmi-Friedman et al., 2000; Ishiko et al., 2001). The majority of mutations affect either the helix initiation domain or termination domain in the central alpha-helical rod domain of K1 or K10 (Fig. 1). There are some genotype-phenotype correlations. Palmoplantar involvement occurs more often in the individuals with a K1 mutation than those with a K10 mutation (DiGiovanna and Bale, 1994) and mild forms of BCIE are associated with a mutation in the L12 linker domain of K1, H1 domain of K1, and more central sequences of

Table 1. Human diseases of keratins.

KERATINS	DISEASES
K5, K14	Epidermolysis Bullosa Simplex
K1, K10	Bullous Congenital Ichthyosiform Erythroderma
	Palmoplantar Keratoderma
K9, K1	Epidermolytic
K1	Diffuse non-Epidermolytic
K16	Focal non-Epidermolytic
K1	Ichthyosis Hystrix type Curth-Macklin
K2e	Ichthyosis Bullosa of Siemens
	Pachyonychia Congenita
K6a, K16	Jadassohn-Lewandowsky form
K6b, K17	Jackson-Lawler form
K17	Steatocystoma Multiplex
K4, K13	Oral White Sponge Nevus
K3, K12	Meesmann's Corneal Dystrophy
K18	Cryptogenic liver cirrhosis
hHb6, hHb1	Monilethrix

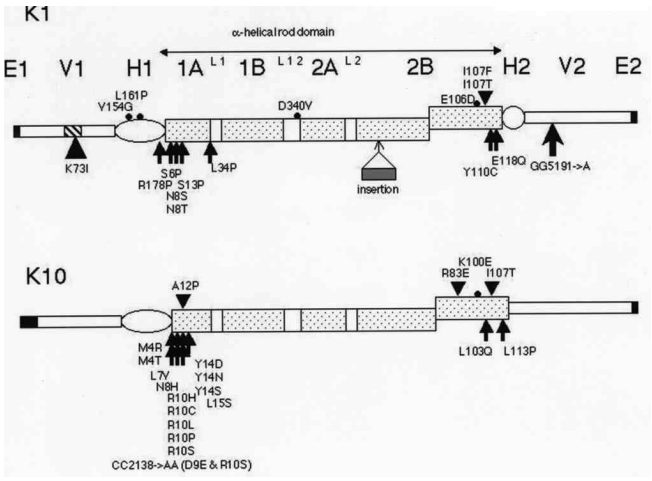


Fig. 1. Structural features of K1 and K10, with localization of disease-associated mutations. All keratins have a central rod domain comprising helical coiled-coil segments (designated 1A, 1B, 2A, 2B) interrupted by non-helical short linker segments (L1, L12, L2). The central region is flanked by the homologous regions H1 and H2 (the latter in type II keratins only) and by variable length end domain sequences that can generally be subdivided into end sequences (E1, E2) and variable regions (V1, V2). The conserved 22 residue-segment (stripes) is shown in the V1 domain of K1.

Small arrows and dots denote mutations associated with typical and mild cases of bullous congenital ichthyosiform erythroderma, respectively. Small arrowheads denote mutations found in annular epidermolytic ichthyosis. An eighteen amino acid insertion into 2B rod domain of K1 caused by a splice site mutation found in epidermolytic palmoplantar keratoderma is also indicated. A large arrowhead in the V1 domain of K1 denotes the mutation associated with non-epidermolytic palmoplantar keratoderma. A large arrow in the V2 domain of K1 denotes the mutation found in ichthyosis hystrix type Curth-Macklin.

2B than the helix termination sequence of K1 or K10 (Chipev et al., 1992; Syder et al., 1994; Yang et al., 1994, 1999a; Kremer et al., 1998).

A distinct phenotypic variant of BCIE, known as annular epidermolytic ichthyosis is also caused by a mutation in the rod domain of K1 or K10 (Joh et al., 1997; Suga et al., 1998; Michael et al., 1999; Sybert et al., 1999; Yoneda et al., 1999). Affected individuals manifest blistering in early childhood followed by recurrent polycyclic erythematous plaques. Palmoplantar skin is hyperkeratotic in the patients with a K1 mutation, but not in those with a K10 mutation. The histopathology of the plaques demonstrates epidermolytic hyperkeratosis in the superficial spinous and granular layers.

Epidermolytic palmoplantar keratoderma (PPK)

PPK defines a group of highly heterogeneous disorders characterized by severe thickening of the stratum corneum of palms and soles. PPK disorders have been classified according to their phenotypic characteristics. The diffuse PPK shows uniform thickening of the palms and soles, which is distinct from focal, striate or punctate PPK. Two major forms of diffuse PPK are epidermolytic PPK and non-epidermolytic PPK. Diagnosis of the former depends on histological detection of epidermolytic hyperkeratosis. In the majority of patients, mutations in K9, a unique keratin exclusively expressed in the palm and sole skin, are detected. An exception is a mutation in the exon 6 splice donor site of K1 (4136G→A) that resulted in epidermolytic PPK in three autosomal dominant kindreds (Hatsell et al., 2001) (Fig. 1). This mutation results in the insertion of 18 residues into the 2B rod domain. In these patients, epidermolysis was not identified by light microscopy, but electron microscopy showed cytolysis in a minority of keratinocytes in the upper spinous and granular layers. The tonofilaments formed tight clumps or aggregates.

Non-epidermolytic PPK

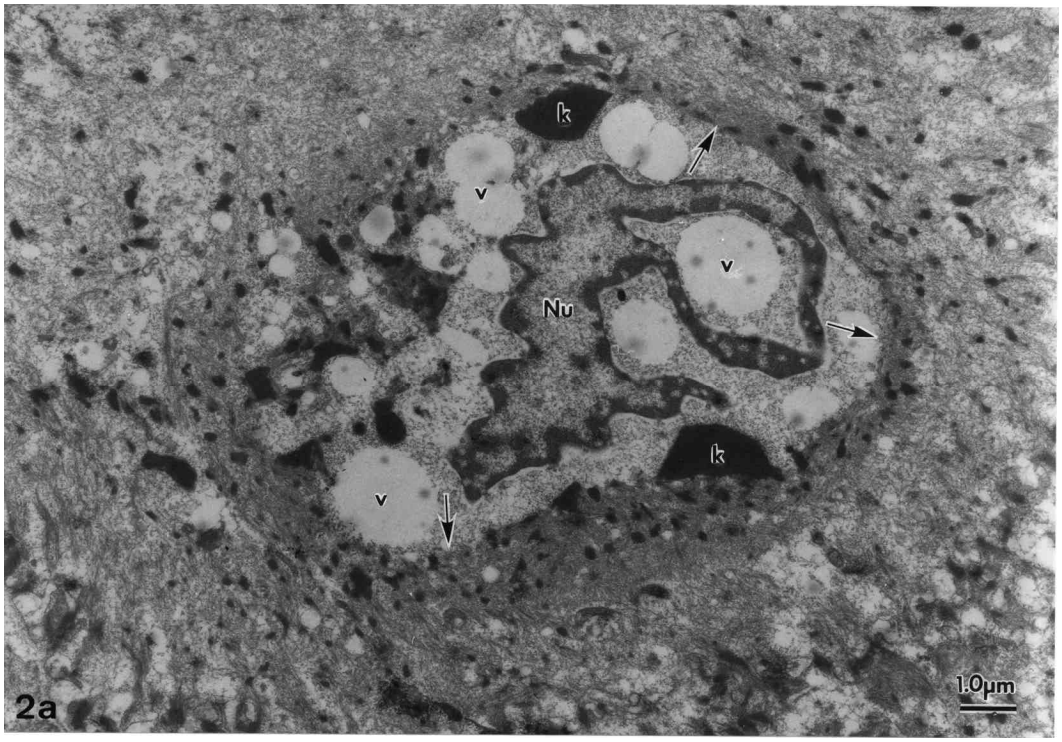
Genetic bases of diffuse non-epidermolytic PPK are less well characterized. A K1 mutation was identified in one family (Kimonis et al., 1994) (Fig. 1), where a single base change in the V1 subdomain of K1 led to a lysine to isoleucine substitution. In this family, 13 members were affected with the pattern consistent with autosomal dominant inheritance. The disease was manifested as moderate to severe thickening of the palms and soles. Hyperkeratosis of knuckle pads of the dorsal aspects of the finger joints, umbilicus and nipple areolae, and mild thickening and dryness of knees and elbows were also observed.

Ichthyosis Hystrix type Curth-Macklin (IHCM)

IHCM is a rare autosomal dominant genodermatosis. Only three families and several sporadic cases have been reported since its first description in 1954 (Curth and Macklin, 1954; Pinkus and Nagao, 1970; Ollendorff-Curth et al., 1972; Anton-Lamprecht et al., 1981; Kanerva et al., 1984; Niemi et al., 1990; Sprecher et al., 2001). Clinical expression varies markedly even within a single family, ranging from localized keratoderma to generalized skin involvement with spiky or verrucous hyperkeratosis. Although palms and soles show severe hyperkeratosis in some cases, including the original patients described by Curth and Macklin (Curth and Macklin, 1954; Anton-Lamprecht et al., 1981; Sprecher et al., 2001), these sites are not affected in others (Kanerva et al., 1984; Niemi et al., 1990). Unlike BCIE, blister formation does not occur in IHCM.

Histologically, severe hyperkeratosis, papillomatosis, and granular cells with perinuclear edema are seen in the epidermis. The most characteristic feature is peculiar cytoskeletal abnormalities in the keratinocytes detected by electron microscopy (Pinkus and Nagao, 1970; Anton-Lamprecht et al., 1973; Kanerva et al., 1984; Niemi et al., 1990; Sprecher et al., 2001) (Fig. 2). Specifically, a unique concentric unbroken "shell" is seen surrounding the nucleus in differentiated keratinocytes, but not in the basal cells. The shells are composed of loosely arranged 10 nm filaments lacking any tendency to form bundles. These filaments in shells are immunoreactive to keratin antibodies, indicating that these are abnormally arranged keratin filaments (Sprecher et al., 2001). This is often associated with perinuclear vacuolization and formation of bi-nucleated keratinocytes. In the periphery of the shells, the filaments form short bundles and terminate in desmosomes. These characteristic abnormalities in cytoskeletal filaments and nuclei have also been detected in the apparently normal-looking skin of a patient, consistent with a primary disease anomaly rather than a secondary reactive change (Niemi et al., 1990).

Recently we have disclosed the molecular basis of IHCM in one family (Sprecher et al., 2001). Initially the skin condition in this family was tentatively diagnosed as Vohwinkel's mutilating PPK, another autosomal dominant disease characterized by diffuse PPK and formation of constricting bands in the digits (Cole et al., 1984). In this family, five members in three successive generations developed hyperkeratosis on the palms, soles and over the joints of extremities. Ainhum-like constrictions of the digits were also noted in three of them. One member had hyperkeratotic lesions on the neck, chest and trunk. Although it may not be easy to differentiate clinically IHCM from Vohwinkel's keratoderma, ultrastructural examination provides clear differences. The suprabasal epidermal keratinocytes of a patient in this family showed the typical diagnostic feature of IHCM (Fig. 2). A heterozygous mutation was then disclosed in exon 9 of the K1 gene (5191GG→A) affecting the V2 domain (Fig. 1). This results in a frameshift, leading to the expression of K1 protein possessing a mutant tail domain. Previous genetic



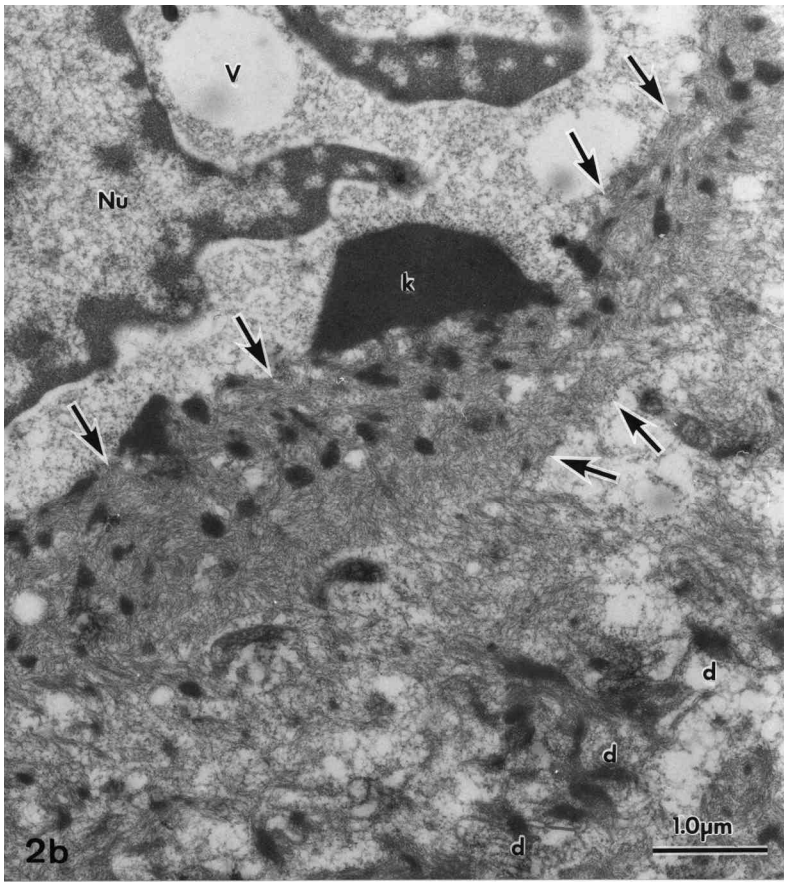


Fig. 2. Electron microscopy of ichthyosis hystrix type Curth-Macklin. Low **(A)** and higher **(B)** magnification. A granular cell with perinuclear vacuoles (v) and a shell-like structure of loosely arranged filaments (arrows). Filaments are connected to desmosomes (d). Nu: nucleus.

linkage analysis excluded the asscocitation between the keratin gene loci and IHCM in a single pedigree with mild phenotypes and without involvement of the palms and soles (Bonifas et al., 1993). This suggests genetic heterogeneity in IHCM.

Implications of keratin diseases in keratinocyte biology

Morphological changes seen in the diseases with different mutations of K1/10 provide insight into our understanding of the function and role of keratins in differentiating epidermal keratinocytes

Keratins provide mechanical strength within keratinocytes

Mutations in the rod domains of K1 and K10 and in the H1 domain or L1/2 linker domains of K1 dominantly disrupt keratin filament assembly and cause of blistering in the upper epidermis and hyperkeratosis in BCIE. This indicates that the keratin cytoskeleton provides mechanical integrity within differentiated epidermal cells and that compromising its structural rigidity through mutations in these domains critical for structural integrity further affects cellular differentiation resulting in abnormal piles of cornified cells. The reason for the migratory annular and polycyclic lesions seen in the annular epithermolytic icthyosis variant is not yet clear.

Although K1 is expressed all over the body surface, an insertion mutation of 18 amino acid residues into the 2B rod domain of K1 is manifesed as a mild form of epidermolytic PPK (Hatsell et al., 2001). Histologically, keratin filaments were clumped, but not leading to extensive cell lysis. This indicates that mutations in a more central part of the rod domain of K1 do not hamper filament assembly and/or stability as compared to those in the helix initiation and termination sequences. In addition, it seems that the palms and soles have a greater dependence for their mechanical integrity through K1, more significantly so than in other body sites.

Keratins as components of the cornified cell envelopes

The Lys-73 residue mutated in a form of non-epidermolytic PPK is within a sequence that is highly conserved among most type II keratins. K1 is crosslinked by transglutaminases to the cornified cell envelopes through this lysine residue (Candi et al., 1998). The cornified cell envelope is a highly insoluble structure formed at the inner surface of the plasma membrane, serving a vitally important barrier function for the tissue and organism (Ishida-Yamamoto and Iizuka, 1998). The cornified cell envelopes are composed of a number of different proteins including keratins. However, the function of each component is not well understood. The missense mutation in this essential lysine amino acid would be expected to lead to a failure of cross-linking of keratin filaments to the proteins of cornified cell envelopes (Candi et al., 1998). Histologically, altered organization of keratin filaments subjacent to the cell envelope and abnormal shapes of the cornified cells were characteristic (Candi et al., 1998). In the granular cells where assembly of the cornified cell envelopes is initiated, keratin filament bundles were separated from desmosomes and the cell periphery, forming microclefts or vacuolar inclusions. The boundary between the uppermost granular layer and the first cornified cell layer was irregular in shape with deep interdigitaions between the two layers. These data suggest that the mutation from lysine to isoleucine has a dominant negative effect on macromolecular interactions involving keratin filaments, desmosomes, and cornified cell envelopes, resulting in a distortion in the shape of keratinocytes. This also suggests functional significance of keratins as a component of cornified cell envelopes.

Keratins as a possible "guide" for other molecules

The structural abnormalities resulting from the one described mutation in theV2 domain of K1 found in IHCM were quite distinct from those associated with other K1 mutations. The V2 domain mutation did not inhibit keratin intermediate filament formation, but altered the higher structural integrity changing the intermediate filament network from a normal cage-like structure into a shell-like appearance. *In vitro* assembly studies and cell transfection experiments of intermediate filaments with headless and tailless variations of keratins have demonstrated that the V2 domain is not essential for intermediate filament oligomerization, assembly, and alignment (Fuchs and Weber, 1994). Our *in vitro* assembly assay using mutant K10 with analogous changes of the V2 domain to that in mutant K1 of IHCM, further confirmed that the assembly of keratin filaments does not depend on the structural integrity of the V2 domain (Sprecher et al., 2001). IHCM keratinocytes express both wild- and mutant-K1, suggesting that the mutant V2 dominantly interferes with normal K1 function. The peculiar, shell-like accumulation of interwoven keratin filaments indicates a failure of higher structural organization of keratin intermediate filaments into tonofibrils.

The V2 domains of K1 and K10 are exceptional in that they are glycine-rich and have a repetitive loop-structure called a "glycine loop" (Steinert et al., 1991). Our protein modeling of the V2 domain of K1 showed an extended, "tentacle-like", protruding conformation (Sprecher et al., 2001). Interestingly, a similar motif is present in other proteins, including loricrin, a major constituent of cornified cell envelopes (Ishida-Yamamoto et al., 1998). Functions of these glycine loop domains are not well understood. Steinert et al. (1991), however, suggested that multiple interactions between the neighboring glycine loops on various adjacent protein molecules form the basis for adaptable intra-cytoskeletal and envelope-cytoskeletal interactions. It was proposed that the glycine loop sequences form weak

hydrophobic interactions between the numerous glycines and H-bonds between keratin filaments and loricrin of the cell envelopes. Such individually weak and reversible interactions are analogous to adhesion mediated by Velcro and this concept has been called the "Velcro hypothesis".

Nothing is known about the mechanisms by which loricrin molecules are positioned near the plasma membrane for cross-linking into the cornified cell envelopes. In normal skin, loricrin is first expressed in the most superficial granular cells. It is associated with keratin filaments and desmosomes to which keratin filaments are inserted (Ishida-Yamamoto et al., 1996) (Fig. 3A). Structural analyses in IHCM have disclosed an impeded translocation of loricrin to the desmosomal attachment plaques (Sprecher et al., 2001) (Fig. 3B). This suggests that a proper interaction between loricrin and the K1 tail domain is required for the localization of loricrin at desmosomes. In this context, it is interesting to note that tonofibrils can move slowly both towards and away from the cell periphery (Yoon et al., 2001), which is compatible with a role of keratin as a "guide" for other intracellular molecules. We propose that the interaction between the glycine loops of keratins and loricrin works not only on the cornified cell envelopes, but also within the cytoplasm and at the desmosomal

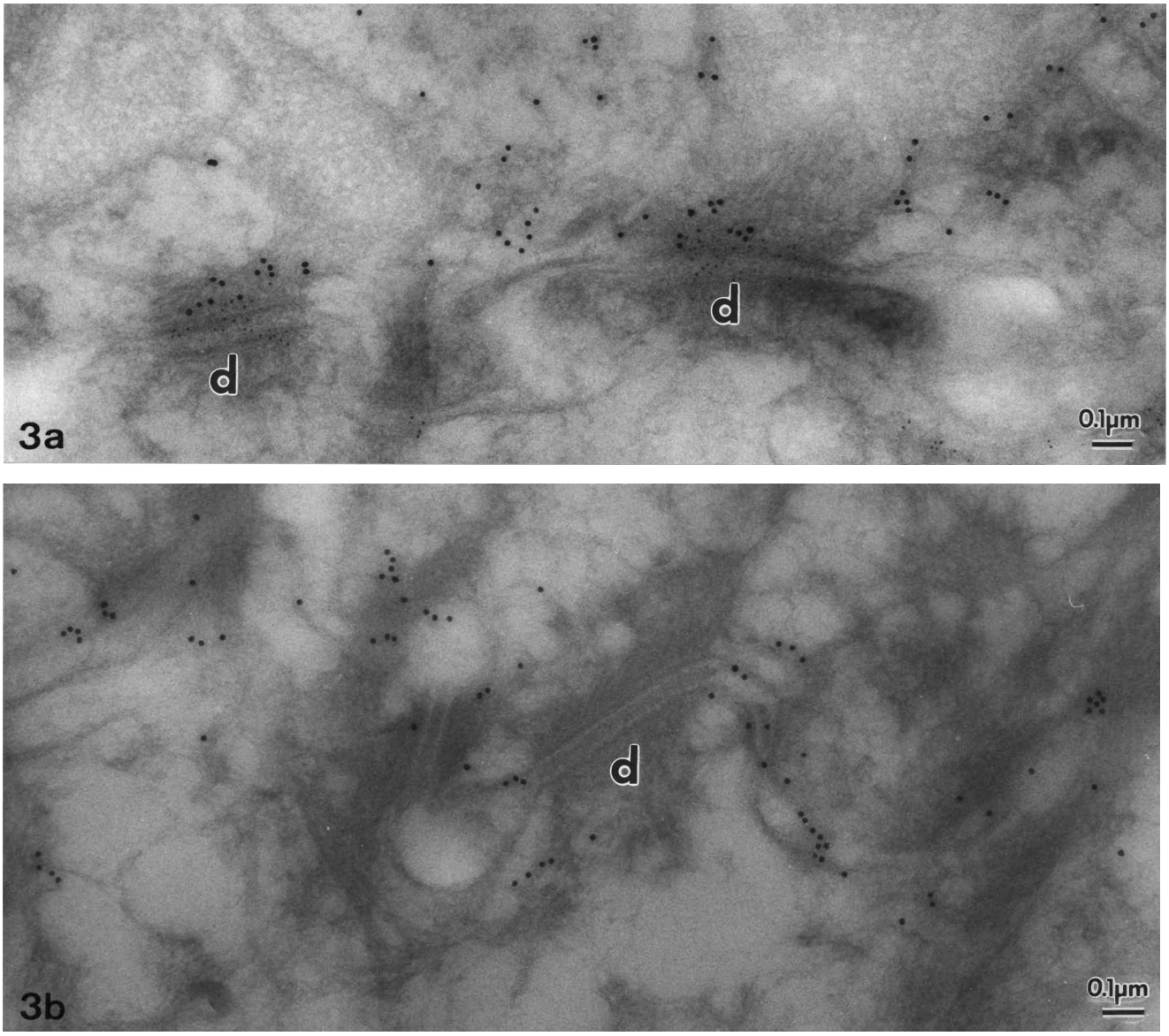


Fig. 3. Immunoelectron microscopy. **a.** In normal skin, loricrin labels are associated with desmosomes (d). Double staining of desmoglein (5 nm gold) and loricrin (10 nm gold). **b.** In a patient with ichthyosis hystrix type Curth-Macklin with the 5191GG→A mutation of K1, loricrin labels (10 nm gold) are sparse at the desmosome areas. x 65,000

attachment plaques. The reason why there are so many tissue-specific keratins is not well understood. However, it is conceivable that there are specific qualitative requirements for the cytoskeleton in different epithelia and under different cellular circumstances. Expression of K1/K10 with their glycine-rich end domains might be a tissue-specific requirement for the efficient assembly of cornified cell envelopes.

Conclusion and future prospect

As revealed by the delineation of distinct K1/K10 mutations in skin diseases with various phenotypes, the nature and the specific location of mutations are critical determinants of the clinical and histological manifestations. These various manifestations have disclosed a major role for keratins as 1) a cytoskeletal framework providing mechanical integrity to the cells, 2) a component of cornified cell envelopes that determines the shape of cornified cells and provides a protective barrier against the environment, and 3) a potential "guide" for other intracellular molecules. Recently an increasing number of keratin- or intermediate filament-associated molecules has been identified (Fuchs and Cleveland, 1998; Fuchs and Yang, 1999). Furthermore, connections between intermediate filaments and actin or microtubules have also been detected. These observations suggest a potentially even more complex function for keratins than previously thought. Further studies in human skin diseases of keratins and their animal models will provide insights for better understanding of keratin biology and disease mechanisms, and for improving therapeutic strategies for keratinization disorders.

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