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Keratin diseases

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The recent discovery that epidermal fragility syndromes can be caused by mutations in the genes for keratin intermediate filaments has been a turning point for research into these structural proteins. Clustering of pathogenic mutations implies differential structural sensitivity along the keratin molecule, and implications for filament function require a new look at culture assay systems, plus a reassessment of structural defects in epithelia and other tissues.

Current Opinion in Genetics and Development 1994, 4:412–418

Introduction

The variable expression of intermediate filaments throughout the body, from massive amounts in barrier tissues to very small amounts in internal tissues or solitary cell types, has led to predictions that these filaments play a significant structural role in the three-dimensional organization of the whole animal. Until the past couple of years, however, this has not been testable directly.

All the protein products of the 50 or so separately identifiable intermediate filament genes share a common structural organization (illustrated in Fig. 1). This is a long, thin α-helical rod domain with non-helical ends, which assembles through a dimeric coiled-coil. From dimers to tetramers and oligomers, these subunits twist and pack together to form microscopic ropes which are woven together in different ways (probably depending on the character of the non-helical ends) to form a network in the cytoplasm and nucleus of virtually all cell types. In humans, at least three-quarters of all intermediate filament proteins are keratins (type I and type II); these are major structural components of epithelial tissues, and their cytoplasmic meshwork connects cells to each other by interlinking with desmosome junctions at the cell periphery.

Recent discoveries of pathogenic mutations in keratin genes demonstrate an unequivocal ‘cytoskeleton’ function for this kind of intermediate filament. In people with epidermal fragility syndromes, the keratinocytes rupture upon relatively mild physical trauma. The mutations thus appear to compromise the ability of the filament network to resist stress and compression effectively, so that the cytoskeleton function is no longer sufficiently protective. In this review, I summarize the findings from epidermal diseases that have brought us to the view that intermediate filaments define the physical resilience of cells and body tissues.

Discovery of keratin diseases

As happens so often in science, the breakthrough in understanding keratin intermediate filament function came from several directions at once; three studies carried out simultaneously and independently used convergent approaches. Fuchs’s research group were conducting experiments with truncated keratins in cells [1,2] and then in transgenic mice [3], whence the phenotypic resemblance to human blistering diseases led them to seek, and identify, mutations in human keratin genes [4]. Epstein’s research group discovered the keratin mutations through linkage analysis of families affected by hereditary skin blistering [5]. Our research group found keratin mutations by first using antibodies to analyze the defective gene products, and then sequencing the epitope-selected regions [6,7**]. All three observations led to the same conclusion: defects in the keratin cytoskeleton lead to fragile keratinocytes, cells that cannot resist the wear and tear of the most exposed tissue of the body. These findings have been followed by a wave of renewed interest in keratins, leading to a new generation of research on the cytoskeleton.

Many mutations and several diseases

Keratin mutations have been identified in at least four types of epidermal fragility syndrome: epidermolysis bullosa simplex (EBS), bullous (congenital) ichthyosiform erythroderma (BCIE or epidermolytic hyperkeratosis [EH] as it is frequently called in the USA), epidermolysis palmo-plantar keratoderma (EPPK) and ichthyosis bullosa of Siemens (IBS). All four are usually inherited as autosomal dominant traits, with rarer examples of recessive forms now being recognized [8*,9]. The list will probably be longer before the year is out.

Abbreviations

BCIE—bullous (congenital) ichthyosiform erythroderma; DM—Dowling-Meara; EBS—epidermolysis bullosa simplex; EPPK—epidermolysis palmo-plantar keratoderma; IBS—ichthyosis bullosa of Siemens; K—Kobner; WC—Weber-Cockayne.
In EBS, the skin blisters easily because basal keratinocytes rupture upon physical trauma such as scratching or rubbing. Keratin mutations in EBS all involve either keratin K5 or K14, the two primary keratins synthesized by undifferentiated keratinocytes of the basal layer (proliferative compartment) of the epidermis. This correlates with the observed basal cell lysis seen in EBS and suggests that the cell fragility is a direct result of a change in the cytoskeleton.

Three clinical forms of EBS are recognized, although the boundaries between them may be largely artificial, as these variants now appear to be part of a graded continuum of severity. The Dowling–Meara variant (EBS-DM or EBS herpetiformis) is the worst form, with clusters of fluid-filled blisters forming anywhere on the body, and skin on the palms and soles is often thickened. Conclusive diagnosis depends on electron microscopy to detect the presence of electron-dense bodies in the cytoplasm, now known to be unpolymerized keratin. Keratin mutations which have been identified from EBS-DM patients are listed in Table 1.

The two other variants are the Köbner (EBS-K) and Weber–Cockayne (EBS-WC) forms. EBS-K blisters are not clustered, but occur over the whole body surface. EBS-WC is the mildest form of EBS; blisters are less frequent and the phenotype is commonly restricted to thickened skin on the palms and soles, presumably as these are the areas where pressure and abrasion are greatest. Keratin mutations found in EBS-K and EBS-WC patients are listed in Table 1.

The frequency of EBS in the UK is usually estimated as one in 50,000, but it is not possible to give accurate figures. The mildest versions of EBS-WC will go unrecorded and will merge with the phenotypic variety of the increasing number of polymorphisms that are now being identified within keratins [10,11,12]. Although EBS conditions can be very distressing and socially stigmatizing, they are not usually fatal, except sometimes in small babies (EBS-DM) in which fatalities are often caused by secondary infection. Many cases of EBS are said to improve with age, and some are said to improve with raised or lowered ambient temperature [13].

This clinical picture contrasts EBS with the more life-threatening forms of epidermolysis bullosa, junctional and dystrophic epidermolysis bullosa, which are diseases of collagens and extracellular matrix molecules and are not connected with keratins.

Epidermolytic hyperkeratosis is a phenotype associated with several keratin skin diseases, including BCIE, EPPK and (just now joining the list of keratin diseases) IBS. These are also epidermal fragility syndromes, but with a different clinical phenotype from EBS. In BCIE, blisters and erythroderma can be extensive in small babies and can sometimes even resemble junctional and dystrophic epidermolysis bullosa. As the child grows, hyperkeratotic thickened skin develops, especially at flexures. All cases of BCIE in which keratin mutations have been identified have involved the genes for K1 and K10, the major secondary or differentiation-specific keratins of the epidermis. Specific mutations are listed in Table 1.

EPPK is clinically similar to BCIE, although the damaged and thickened skin is restricted to palms and soles. Recent data indicate that at least some of these patients have mutations in the recently characterized epidermal keratin K9, which is reported to be specifi-
Genetics of disease

Table 1. Keratin diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Variant</th>
<th>Keratin</th>
<th>Mutation</th>
<th>Cluster no.</th>
<th>No. cases</th>
<th>Reference</th>
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<td>2</td>
<td>1</td>
<td>[4]</td>
</tr>
<tr>
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<td>[4]</td>
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<tr>
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<tr>
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<td>2</td>
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<td>1</td>
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<tr>
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<td>1</td>
<td>[21*]</td>
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<td>Ser185→Pro</td>
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<td>1</td>
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<td>1</td>
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<td></td>
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<td>Ser192→Pro</td>
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<tr>
<td>EPPK</td>
<td>K9</td>
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<tr>
<td></td>
<td>K9</td>
<td>Arg162→Cln</td>
<td>2</td>
<td>1</td>
<td>[46*]</td>
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<td>Asn160→Alys</td>
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<td>6</td>
<td>2</td>
<td>[16]</td>
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</table>

Characteristics of keratin diseases. EBS—epidermolysis bullosa simplex; DM—Dowling-Meara; WC—Weber-Cockayne; K—Köbner; BCIE—bullous lichenoid ichthyosis; EB—epidermolysis bullosa; EH—epidermolysis bullosa; EPPK—epidermolysis bullosa; FPD—epidermolysis bullosa; IBS—ichthyosis bullosa of Siemens.

Superficial keratinocyte layers [15*], thus accounting for the IBS phenotype [16].

Beyond these documented mutations in keratins it would be astonishing, given the total number of intermediate filament genes, if intermediate filament diseases were not found in tissues other than skin. However, such mutations have yet to be identified conclusively.

**Mutations in keratins are clustered**

A number of features emerge from the list of mutations affecting keratins (shown in Table 1). First, the distribution of mutations along the keratin sequences is non-random, being clustered around certain loci; six mutation clusters have emerged so far [17*] (Fig. 1). Second, irrespective of the phenotypic differences between clinically recognized keratin diseases involving different keratin genes, the keratin mutations fall into the same cluster boxes along the consensus protein structure. Third, the clusters can be divided into two groups, severe or mild, associated with greater or lesser severity of the disease phenotype. The clusters have been numbered from the amino terminus towards the carboxy terminus (see Fig. 1).

**Cluster site 1**

The first cluster of mutations affects the H1 domain in the head region (type II keratins only). These mutations mostly introduce additional potential phosphorylation sites [18–20] and in EBS show a mild phenotype. Phosphorylation sites in the H1 domain are thought to be used to regulate the polymerization state of intermediate filaments, for example during meiosis. It is not yet known whether these supernumary sites are phosphorylated in vivo.

**Cluster site 2**

The second cluster of mutations affects the helix initiation motif, which is conserved within intermediate filament subclasses (type I, type II etc.). This is by far the most frequently mutated site identified in keratin diseases so far. 50% of all the keratin mutations identified affect the tenth residue in helix 1A of type I keratins, which in EBS is always associated with a severe phenotype. A similar mutation has been reported in a type II keratin [21*]. Some of these mutations, but not all, involve a CpG dinucleotide [11*,22*]. The relatively high number of mutations at this site may reflect a residual sampling bias, as some studies screened only for mutations affecting the two ends of the rod domain.

**Cluster site 3**

The second half of helix 1A may be affected by another mutation cluster, but this is associated with a mild dis-
ease phenotype [8*,23]. This region is less conserved than the helix initiation motif.

Cluster site 4
Another mutation cluster site affects the L12 linker domain, mutations being associated with a mild disease phenotype [17*,24]. Little is known of the function of linker domains; experimental manipulation of the L12 domain sequence has not revealed any reproducible functional characteristics.

Cluster site 5
The helix 2B cluster is a looser collection of several mutations found on the carboxy-terminal side of the conserved heptad polarity reversal, or ‘stutter’ (see Fig. 1), and before the helix termination motif. These are associated with a mild disease phenotype [25,26*,27,28*].

Cluster site 6
The helix termination motif (the last 13–15 residues of the consensus rod domain) is the most highly conserved motif in intermediate filament sequences. Mutations affecting this peptide are associated with a severe disease phenotype. In comparison with the boundary peptide at the amino-terminal end of the rod domain, however, fewer mutations are found here than at site 2 [7*,16,29*]. Mutations affecting amino acids just outside this peptide give a mild disease phenotype.

Disease severity is linked to mutation cluster site
As can be seen from the above, the more severe phenotypes of the EBS diseases are linked with mutations in the two helix boundary peptides, and the milder forms (EBS-WC and EBS-K) are associated with mutations at other sites. Many lines of experimentation had already demonstrated the importance of these boundary peptides [1,2,30,31], so these observations have been rapidly accepted. Such distinctions are less easy to make for the BCIE diseases, as mutations between the rod ends have not been characterized. Suprabasal keratins polymerize on a template of basal-synthesized K5 and K14, and it may be that only ‘severe’ classes of mutations in K1/K10 are pathogenic.

Mutation clusters suggest zones of particular fragility, or points at which the molecular interactions are exquisitely specific, and which are intolerant of sequence variation. In most cases, these points are in areas of high sequence conservation. The apparent absence of mutations from other regions may reflect bias because of small sample numbers (future work will clarify this), lack of any pathological impact elsewhere in the sequence (to be clarified by sequencing ‘normal’ keratins to assess variation in the population), lethality (which seems unlikely at present), or low mutability of the DNA in these regions (this can be examined by sequencing pseudogenes, as mutations will accumulate with time in these silenced genes [32]).

Effects of mutations on the filament cytoskeleton
Keratin assembly starts with heterodimerization of type I and type II proteins [33,34] (other intermediate filaments form homodimers). Early stages of assembly are unlikely to be affected by the described pathogenic mutations, as keratin molecules which cannot dimerize are rapidly degraded [35]. Polymerization proceeds rapidly in multiple directions from heterodimeric or trimeric ‘soluble’ particles to produce a filament with no overall polarity. Attempts to understand how this packing proceeds have produced several useful but incomplete models relating to rod domain interactions. Many models suggest critical interactions between the helix boundary peptides [36,37*,38*]. Most of the mutation clusters can be aligned with the proposed overlap zones in recent packing models [38*], although the fit is not yet perfect. Any reduction in affinity between interacting subunits of the filament could make the filament network more friable, less resistant to deformation, or slower to reassemble after cytoplasmic remodelling.

Only one region outside the rod domain has been implicated in keratin diseases, and that is the H1 pre-helix subdomain which is absent from type I keratins. Information on how the non-helical heads and tails interact during filament polymerization in vivo is still patchy. We do know that the H1 domain is essential, as without it filaments are not formed [35,39–41]. This region contains phosphorylation sites; hyperphosphorylation prevents polymerization in vimentin, solubilizes lamins and is suspected of destabilizing keratins during mitosis. Three mutations identified in the H1 domain of keratins K5 [18,20] and K1 [42*] (see Table 1) all introduce potential new phosphorylation sites; the effect of a fourth mutation here is unclear [43]. Raising the background phosphorylation level would presumably destabilize keratin filaments in interphase, as hyperphosphorylation is believed to do during mitosis.

Conclusions
At least three conclusions can be drawn from the findings presented here. First, the prediction of a structural role for intermediate filaments was evidently correct. The function of the intermediate filament system as a ‘cytoskeleton’ within the cell can be visualized using the analogy of a balloon (the cell) with a box inside it (the cytoskeleton). If the box is rigid, the balloon can be compressed and the box takes the strain, but if the box is too small, or fragile, or missing, as in a defec-
tive cytoskeleton, then the balloon will burst under the pressure (Fig. 2). This functional model requires that researchers use a different approach to assaying intermediate filament function in cultured cells and \textit{in vitro} polymerization systems.

![Diagram of normal and abnormal keratin cytoskeletons](image)

Fig. 2. Model describing the function of the keratin cytoskeleton in resisting compression and stress on a cell. (a) Normal keratin cytoskeleton. The cell is visualized as a balloon with a box inside representing the cytoskeleton. On compression or distortion, the internal box will absorb the strain and prevent the balloon from bursting. (b) Abnormal keratin cytoskeleton. The box is too fragile, too small, or absent, so that under pressure, the cell will collapse.

Second, even subtle sequence heterogeneity in intermediate filament proteins can be very significant, as demonstrated by the dramatic effects of a strategically placed point mutation. Sequence variations between members of the intermediate filament multigene family have evolved to adapt these structural proteins to the specific requirements of each cell type in its own functional niche in the body. This implies that the intermediate filament complement of a cell defines, or restricts, its physical capabilities, making this one of the most fundamental differentiated characteristics of a cell. This explains the biological requirement for the tissue-specific expression patterns observed by immunohistochemistry.

Third, evolutionary pressure is still very active on these genes. This is apparent from the role of intermediate filaments in tissues such as skin, plus the high frequency of polymorphisms and pseudogenes that are coming to light from the close scrutiny of keratin sequences being driven by studies of keratin diseases. Keratin genes produce major structural components of the external barrier layer, the skin and its associated structures, which is the primary defense of an organism against infection and injury. They influence the external appearance of the animal (e.g. hair, feather, claw and horn keratins) and therefore affect mate selection and reproductive success. Keratin genes have evolved by a process of duplication and divergence [44] which is still ongoing, as seen from the evolutionary drift in sequence variations of the many 'silent' conventional pseudogenes for keratinocyte keratins [32, 45]. Duplicated genes must provide the potential starting material for the evolution of new keratins.

Finally, besides the generation of data on an interesting problem, the study of keratin diseases has produced three other side effects: the sudden and frequent appearance of reviews on intermediate filaments (all with very short life expectancies), an unprecedented surge in the interest in dermatology within the scientific community, and the development of collaborative bonding between clinicians and scientists at a speed that no government initiative could ever achieve.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


The only characterized recessive keratin mutation so far, affecting helix 1A (second half) of keratin K14 (Glu144→Ala), giving a mild mutant phenotype.


Variation in the size of an end domain in polymorphic keratin K1 provides a likely candidate for a functional difference between the two forms, but no known phenotypic consequences have been shown so far.


Mutations identified in helix 1A (Arg156→His in K10) confirm earlier predictions from transgenic mouse experiments by this group that epidermolysis hyperkeratosis (bullaous congenital ichthyosiform erythroderma, BCIE) would also be caused by keratin mutations. Authors discuss the contribution of CPG residues in this codon to the frequent mutations in BCIE and epidermolysis bullosa simplex.


The authors describe polymorphisms in keratins which also provide useful intragenic marker probes.


See [15*].


This paper and [14*] describe keratins with body site specific expression patterns in stratified squamous epithelia, which immediately makes them candidates for genes affected in body site restricted forms of epidermolysis bullosa simplex, bullous (congenital) ichthyosiform erythroderma and related epidermal fragility syndromes. Keratin K9 is expressed in palmo-plantar epidermis, K2e in very superficial skin keratinocytes, and K2p in superficial keratinocytes in cornified oral epithelium (palate).


This paper describes two new mutations (Val127→Met in K14 and Arg331→Cys in K5) in the L12 linker region and establishes a new mutation cluster region in keratins, leading the authors to propose the existence of six mutation cluster sites so far. The L12 mutations are useful, as there are no functional data on the role of the conserved linker domains; the mutations may alter the secondary structure of this linker and may change its flexibility.


The mutations described include the rarer type II helix initiation motif mutations in keratin 1 and a case of phenotypic variation within one pedigree, providing evidence for a multifactorial basis for the BCIE phenotype. Variation did not correlate with polymorphism in the V2 domain. Are other genes involved? Possible effects on keratin structure include weakening the α-helix in 1A.


Out of 10 epidermolysis bullosa simplex cases, five had mutations in the same codon (Arg156) in the helix initiation motif. The authors suggest possible selective methylation to explain the bias of mutations at this residue.


The first spontaneous deletion mutation described in keratins, this one produces a mild phenotype in keeping with its location outside the helix boundary regions.


This paper describes a collection of mutations from both ends of the rod domain and demonstrates the predominance of mutations at cluster site 2 (affecting the helix initiation motif).


One of the first descriptions of mutations in keratins 1 and 10 associated with bullous (congenital) ichthyosiform erythroderma (BCIE).


See [37**].

38. Steinert PM, Marek LN, Fraser RDB, Parry DAD: Keratin Intermediate Filament Structure: Crosslinking Studies Yield Quantitative Information on Molecular Dimensions and Mechanism of Assembly. *J Mol Biol* 1993, 230:436-452. This paper and [37**] describe similar experiments to determine packing arrangements in intermediate filaments; by chemically crosslinking filaments, cleaving them, reversing the cross-linking and sequencing the separated peptides, potential near-neighbour peptide sequences were identified. Results concord with each other, but [38**] is more extensive. Position of the identified peptides within the full sequences suggests close proximity of several combinations of helical segments; [38**] suggests an overlap of both helix boundary peptides.


A Leu160→Pro change in the pre-helix H1 domain is suggested to alter the conformation of the head domain, but also creates a potential additional phosphorylation site, for p34^*cdc^ kinase, in this region, known to be essential for filament assembly and thought to contain important phosphorylation sites to regulate polymerization. The paper describes a useful competitive assembly assay using peptides to test detrimental effect of mutations and also describes more polymorphisms.


This paper represents the first characterization of mutations in EPPK, and the first characterization of keratin mutations in other than the major epidermal keratin genes.


The first documented example of antenatal screening carried out on the basis of a known keratin mutation in the family. The PCR assay was carried out on DNA from chorionic villus sampling, and the (positive) diagnosis was later confirmed by electron microscopy.

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