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Mechanisms of Cell Migration

Guest Editors
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The migration of cells is fundamental to the development and maintenance of organisms, however the complexity involved creates challenges for fully understanding the process. This issue of Essays in Biochemistry includes reviews on membrane dynamics, actin dynamics, cell matrix adhesion, microtubules and modelling of cell migration, as well as others, all illustrating the complex nature of the cell migration process. The cover is a compiled 3D image of keratin (green) and actin (red) filament distribution in a migrating keratinocyte. Image courtesy of Rudolf E Leube.

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Review Article

Keratin intermediate filaments: intermediaries of epithelial cell migration

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Migration of epithelial cells is fundamental to multiple developmental processes, epithelial tissue morphogenesis and maintenance, wound healing and metastasis. While migrating epithelial cells utilize the basic acto-myosin based machinery as do other non-epithelial cells, they are distinguished by their copious keratin intermediate filament (KF) cytoskeleton, which comprises differentially expressed members of two large multigene families and presents highly complex patterns of post-translational modification. We will discuss how the unique mechanophysical and biochemical properties conferred by the different keratin isotypes and their modifications serve as finely tunable modulators of epithelial cell migration. We will furthermore argue that KFs together with their associated desmosomal cell–cell junctions and hemidesmosomal cell–extracellular matrix (ECM) adhesions serve as important counterbalances to the contractile acto-myosin apparatus either allowing and optimizing directed cell migration or preventing it. The differential keratin expression in leaders and followers of collectively migrating epithelial cell sheets provides a compelling example of isotype-specific keratin functions. Taken together, we conclude that the expression levels and specific combination of keratins impinge on cell migration by conferring biomechanical properties on any given epithelial cell affecting cytoplasmic viscoelasticity and adhesion to neighboring cells and the ECM.

Introduction

Migration requires linkage of the force-generating machinery to its counterbalances both within the cell and the outside environment. While the force-generating machinery corresponds to the acto-myosin system, counterbalance is provided by cytoskeletal filaments that are coupled through specific junctions to the extracellular matrix (ECM) and neighboring cells. The cytoskeletal filaments comprise, besides actin microfilaments, microtubules and intermediate filaments (IFs), each with unique biochemical, structural and functional properties. The role of IFs in cell migration has remained enigmatic. Rather than acting as effectors of cell migration, IFs appear to be intermediaries affecting the migratory phenotype in manifold and sometimes even opposing, context-dependent ways by altering cellular viscoelastic properties and by acting as mechanotransducers and mechanosensors [1–4]. Given the limitations of the review, we will restrict it to epithelial keratin intermediate filaments (KFs), although we would like to point out that the mesenchymal IF vimentin is often found alongside KFs in highly motile epithelial cells [4–6]. For information on the contribution of non-keratin IFs to cell migration, we refer the interested reader to excellent and comprehensive recent reviews [1,2,7–9].

In terms of physiology and pathology, movement of cells becomes particularly important in determining epithelial developmental processes, regeneration, wound healing and cancer cell metastasis. All of these events require modulation of the highly abundant keratin cytoskeleton to support the necessary shape changes and to provide the stability needed for directed translocation of the cell body. We will argue that the complex expression patterns of the cytoplasmic KF polypeptides are uniquely suited to fine-tune the mechanophysical properties of epithelial cells during single and collective migration.

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Table 1 Sequence homology classes of intermediate filament polypeptides in human

Type	Name	Main cell type
I	'Acidic' keratins K9, K10, K12-K20, K23-K28	Epithelial cells
	'Acidic' hair keratins K31-K40	Trichocytes
II	'Basic' keratins K1-K8, K71-K80	Epithelial cells
	'Basic' hair keratins K81-K86	Trichocytes
III	Vimentin	Connective tissue cells
	Desmin	Muscle cells
	GFAP (glial fibrillary acidic protein)	Glial cells
	Peripherin	Neurons (PNS)
	Syncoilin	Muscle cells
IV	Neurofilaments H, M, L	Neurons
	α-Internexin	Neurons
	Nestin	Neuroepithelial stem cells
	Synemin	Muscle cells
V	Lamins A, B1, B2, C	Ubiquitous (in nucleus)
VI or others	Filensin	Lens
	Phakinin	Lens

What makes KFs so special?

Keratins are divided into type I and type II polypeptides representing two of four cytoplasmic IF types that are related to the nuclear type V lamin IFs and other, unusual IFs that are referred to as type VI and are produced in the lens (Table 1). In contrast with the rather rigid and stiff tubulin- and actin-based cytoskeletal filaments, IFs are semi-flexible with a persistence length in the range of 1 compared with 7–22 μm for actin filaments and several millimeters for microtubules [10–12]. They are also highly elastic with extensibility up to 3.6-fold before rupture and a Young's modulus of 6–300 Pa compared with 1800–2500 Pa for actin filaments and 1000–1500 Pa for microtubules [12,13]. IFs harden with increasing strain which is referred to as strain-hardening or strain-stiffening conferring the capacity to sense and respond to tension [14]. The molecular assembly and architecture of IFs also differ fundamentally from that of the other cytoskeletal filaments: rod-shaped, instead of globular-shaped, subunits spontaneously form branched networks without nucleoside triphosphates or special chaperones [15–17].

Keratins and other cytoplasmic IF polypeptides have a common domain structure consisting of a structurally conserved central α helical rod domain and highly variable flanking head and tail domains. The ∼310 amino acid-long rod domain is interrupted by the non-helical linkers L1 and L12, separating the rod into subdomain coils 1a, 1b and 2. The rod domain is furthermore characterized by regular heptad repeats containing hydrophobic amino acids at the a and d positions which are the basis of the extremely stable coiled-coil dimer formation. Keratins are obligatory heterodimers, whereby type I keratins align in parallel and in register with type II keratins. Typically, specific type I and type II polypeptides pair. Two heterodimers then associate via a knob-pocket mechanism in an antiparallel and staggered fashion into ∼65 nm-long, rod-shaped non-polar tetramers. Four to eight tetramers assemble laterally into unit-length filaments, which intercalate longitudinally eventually generating mature KFs with the characteristic 8–12 nm diameter (Figure 1; [15,16]; for recent insights on keratin tetramers see also [18]).

Although it is known that biochemical properties vary considerably between different keratins [19,20], direct comparisons are rare and it is still poorly understood how keratin isotype-specific surface charge, post-translational modifications and regulatory functions of the end domains affect atomic fine structure, assembly kinetics, filament bundling and filament branching. Studies have been initiated, however, to assess mechanical properties of specific keratin pairs *in vitro*. Thus, the K8/K18 pair, which is most prominent in simple epithelia, self-assembles into networks with gel-like properties [21]. The resulting network mechanics are determined by attractive interactions between KFs as determined by mechanical rheology and examination of the ion dependency [22–26]. Furthermore, the K5/K14 pair, which is localized in the basal compartment of stratified epithelia, forms mechanically resilient bundles in the absence of cross-linkers [27,28]. The finding that the viscoelastic modulus of *in vitro* assembled keratins differs from that of detergent-extracted cellular keratin networks, however, indicates the presence of cross-linkers in the native environment [29].

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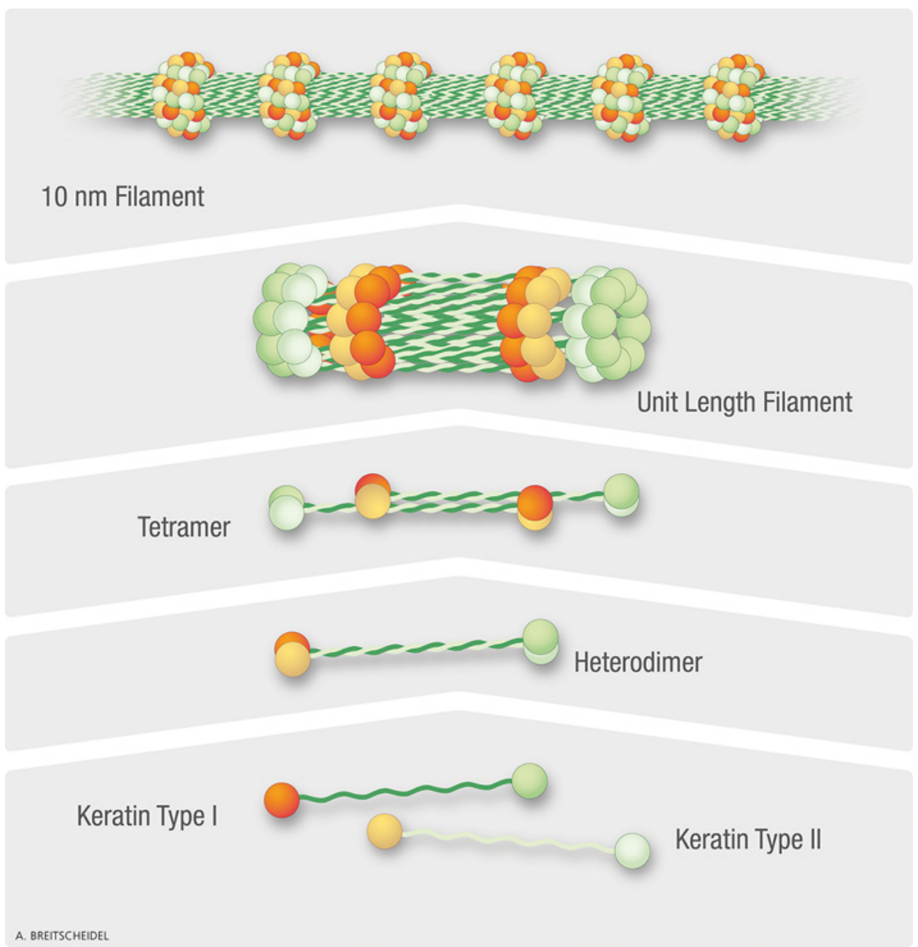

Figure 1. Scheme depicting major aspects of keratin filament assembly

Keratins are grouped into type I and type II. Each keratin polypeptide consists of ∼310 amino acid-long central helical rod domain that is flanked by variable head and tail domains. Dimers form by coiled-coil interactions between the rod domains of a type I and type II keratin polypeptide. The resulting heterodimers subsequently assemble in an antiparallel and staggered fashion into non-polar tetramers. Typically, four to eight keratin tetramers associate laterally to generate the ∼65 nm unit length filament. Unit length filaments elongate by end-on intercalation into 10-nm filaments.

How do KFs affect mechanical properties of epithelial cells?

At present, we are only starting to learn about the exquisite mechanical properties keratins confer on epithelial tissues [30]. A recent paper by Latorre et al. [31] assigns an important rescue function to KFs on stretch-induced dilution of the actin cortex thereby supporting superelasticity of epithelia to sustain extreme stretching. In accordance with the extreme elasticity of individual KFs, the KF cytoskeleton of epithelial monolayers withstands high, i.e. up to 100%, strain [32] suggesting that the KF cytoskeleton is a crucial tension-bearing system under extreme mechanical load. Conversely, lack of keratins or aggregation of keratins leads to cell softening and mitigated cell stiffening [33–36]. Of note, disruption of actin filaments and microtubules has comparatively little effect on keratinocyte mechanics [33,34,37].

Physiologically, the mechanical properties of epithelial cells may be tuned by the expression of specific keratin pairs each providing distinct viscoelastic properties. Thus, K5/K14 in basal epidermal keratinocytes allows cell division and movement of cells to the suprabasal compartment during the physiological differentiation process. Even more, the presence of K5/K14 together with the induction of other keratins, i.e. K6, K16 and K17, appears to be an important feature of cells responding to wounding [38]. Basal keratinocytes extend tongue-like structures from the adjacent intact epidermal epithelium to cover the wound from its edges during wound healing [39,40]. This plasticity and overall capacity for rapid shape changes is lost when basal keratinocytes enter the suprabasal compartment. It is

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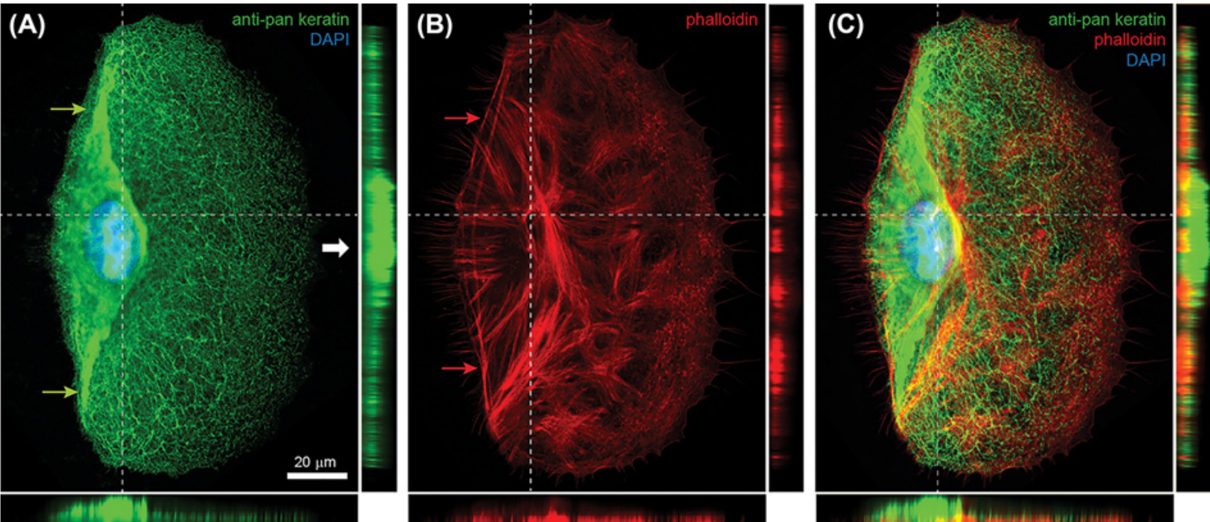

Figure 2. The actin and keratin cytoskeleton segregate with unique distribution patterns in migrating keratinocytes
The projection views depict the fluorescence recorded in a migrating primary human epidermal keratinocyte (direction of migration indicated by white arrowhead) showing the distribution of keratin using a pan keratin antibody (**A**) and filamentous actin using phalloidin (**B**; merged image in (**C**)). The nucleus is demarcated in blue by DAPI staining. Side views of the z-planes denoted by broken lines are also shown. A corresponding 3D animation is presented in Supplementary Movie S1. Note that the keratin network is concentrated around the nucleus with lateral extensions of thick KF bundles forming a mustache-like structure (arrows in A) in the rear part of the cell. KF density and bundle thickness decrease toward the cell front. On the other hand, prominent actin stress fibers are seen in the cell rear (arrows in B) and increased actin staining is seen in the lamellipodial-rich cell front. Scale bar: 10 μm.

coupled to loss of K5/K14 and increased synthesis of K1/K10, which prevent proliferation and impede cell migration both *in vitro* and *in vivo* [41–43].

Association with chaperones and post-translational modifications add another level of controlling the mechanical properties of the keratin cytoskeleton [44–46]. Thus, the small heat shock protein Hsp27 severely affects the assembly dynamics and structure of K8/K18 networks *in vitro*. It was furthermore suggested that K8 phosphorylation lowers the tensile force of the KF network [47] and that inhibition of K18 phosphorylation prevents keratin tortuousness in response to cell stretching [48]. Complex phosphorylation patterns of a single keratin polypeptide may therefore allow precise adjustment of its molecular interactions and viscoelastic properties with high temporal and spatial resolution. This could explain the differential subcellular organization of KF networks. A particularly eye-catching situation is encountered in migrating keratinocytes (Supplementary Movie S1 and Figure 2). These polarized and D-shaped cells have a KF network with a fine mesh size and thin filaments in the leading part, which is flat and rich in highly dynamic lamellopodia and filopodia. Much thicker and bundled KFs occur in the rear part of the cell forming a perinuclear cage with lateral, mustache-like extensions. The different types of network organization likely reflect different functions supporting high plasticity in the cell front needed for lamellipodial exploration and extension and increased resilience in the rear to increase the efficiency of acto-myosin contraction needed for cell body translocation.

An interesting function has been recently proposed for vimentin in migrating cells that may also be of relevance for KFs. Analyses of time-lapse images suggested that vimentin IFs template microtubule formation. Because of the comparatively long half-life of vimentin, the IF template persists to support the directed extension of the short-lived microtubules thereby improving persistence of cell migration and hence enhancing the efficiency of directed cell migration [49]. In accordance, loss of keratins elevates the speed of cell migration but reduces persistence. Conversely, increased keratin expression has opposite effects [50].

How are keratin filaments linked to actin filaments?

To understand the mechanical function of keratins in migrating cells one has to take into account the cross-talk of KFs with microtubules and, most importantly, the contractile acto-myosin apparatus. Physical contact is mediated by static links through large cross-linking molecules and dynamic interactions through motor proteins. Given the limited knowledge on microtubule–keratin interactions [51,52], we will focus on keratin-actin links.

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KFs associate with members of the plakin family including, among others, plectin, epiplakin, periplakin and desmoplakin [53,54]. These large molecules function as cytolinkers by binding to cytoskeletal filaments and components of cell–cell and cell–ECM junctions. Depletion of plakins affects migration albeit in different ways with loss of plectin, periplakin and desmoplakin increasing migration and loss of epiplakin decreasing it [55–59]. It is assumed that these effects are caused by altered KF network organization [55,56,59–63]. Yet, depletion of the major cytoskeletal cross-linker, plectin, has surprisingly little if any effect on cytoplasmic viscoelasticity and KF network dynamics [56,60,64].

The contribution of actin-associated motor proteins to keratin network organization and dynamics can be deduced indirectly from the effects of modulating actin filaments. Disrupting actin filaments leads to major KF network reorganization [51]. Recent co-immunoprecipitation and proximity ligation assays of keratin and non-muscle myosin heavy chain-IIa and far-Western assays of purified proteins suggest that keratins and actin-associated motor proteins interact [65,66]. Furthermore, actin filaments and KFs align in response to cyclic strain allowing them to become more mobile [67].

Although static and dynamic linkages between KFs and actin obviously exist, they appear to be limited. We would therefore like to emphasize another aspect of cytoplasmic network organization, namely the segregation of the bulk of actin and keratins, especially in migrating cells (Supplementary Movie S2 and Figure 2). For the most part, they form separate networks with very little overlap. We therefore propose that, based on their very different biomechanical and chemical properties, both systems act primarily as distinct entities. Actin filaments provide contractile force, rigidity and stiffness whereas KFs provide flexibility, elasticity and resilience at high strain. In migrating cells, compression of the cytoplasmic space and drastic shape changes, which are induced by the cortical acto-myosin system is thereby buffered with the help of the keratin network forming a highly flexible and extensible protective cage around the nucleus and dynamically positioning other cytoplasmic organelles [17,68].

How does the KF–hemidesmosome linkage affect cell migration?

Keratinocyte migration depends largely on remodeling of the actin-dependent focal adhesions (FAs) to the ECM [69]. FAs are highly dynamic and essential pro-migratory structures [70–73]. Much less attention has been paid to keratin-associated hemidesmosomes (HDs), which also mediate contact to the ECM and have a distinct molecular composition (Figure 3; [74,75]). They are considered to be rather static inhibitors of cell migration as suggested from observations in cultured keratinocytes forming HD-like adhesions (HDLAs; [70,71,75]). Recent discoveries, however, have challenged this view revealing dynamic turnover of HDLAs during migration and intricate cross-talk between FAs and HDLAs that regulate overall migratory behavior of cells [76–79]. These findings are in-line with the presence of HDs in the extending tongue of wounded epidermis [80].

A highly ordered pattern consisting of arrays of chevron-shaped keratin-associated HDLAs, which are positive for α6/β4-integrins, BPAG1/BP230 and plectin, and intercalated FAs was recently described in migrating primary keratinocytes (Figure 4A; [79]). Both junctions are spatially segregated but functionally linked through a coordinated assembly/disassembly mechanism, whereby new junctions are formed at the cell front and old junctions are disassembled at the cell rear. This allows maintenance of the central part of the array serving as a stable attachment for the migrating cell to support translocation of the cell body with respect to the ECM. The same HD-FA pattern was also identified in the leader cells of collectively migrating keratinocyte sheets (Figure 4B; [79]), indicative of an important mechanical function since traction force microscopy showed that leader cells exert most of the traction force [81].

Indications for mechanosensing KFs have been collected. Thus, shear stress induces reorganization of the KF network involving phosphorylation [30,82]. A recent publication furthermore links keratin binding of SOLO (ARHGEF40), a RhoA-targeting nucleotide exchange factor, to tensional force-induced cytoskeletal reorganization [83,84]. The mechanosensory function of IFs has been particularly worked out well for the IF-HD scaffold in the hypodermis of *Caenorhabditis elegans*. In this situation, mechanical pressure exerted on HDs is transmitted to IFs via PAK1-mediated phosphorylation, which in turn promotes HD maturation to counteract the external mechanical stress [85]. A mechanosensory role was also suggested for the plectin-mediated vimentin–FA interaction in fibroblast [86]. Whether analogous mechanisms exist for the keratin-HD scaffold and how they are interlinked with epithelial migration remains to be examined.

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Figure 3. The schemes depict major molecular components of HDs (left) and desmosomes (right)
HDs are integrin-mediated structures that are specialized in epithelial cell attachment to the ECM by providing a link between the extracellular basement membrane and the mechanical stress-bearing intracellular KF network. In epidermis, type I HDs can be found, which consist of transmembraneous $\alpha6\beta4$-integrin dimers and BPAG2 (type XVII collagen, COL17A1) that are respectively anchored to K5/K14 IFs via cytolinker plectin 1a and BPAG1e. Desmosomes consist of transmembrane proteins, desmogleins and desmocollins, whose extracellular domains interconnect to form cell–cell adhesion, and their cytoplasmic tails bind to plakoglobin and plakophilins, which are also known as armadillo proteins. These armadillo proteins are then bound to desmoplakin, a cytoskeleton-associated protein, which finally anchors cytoplasmic KFs to desmosomes.

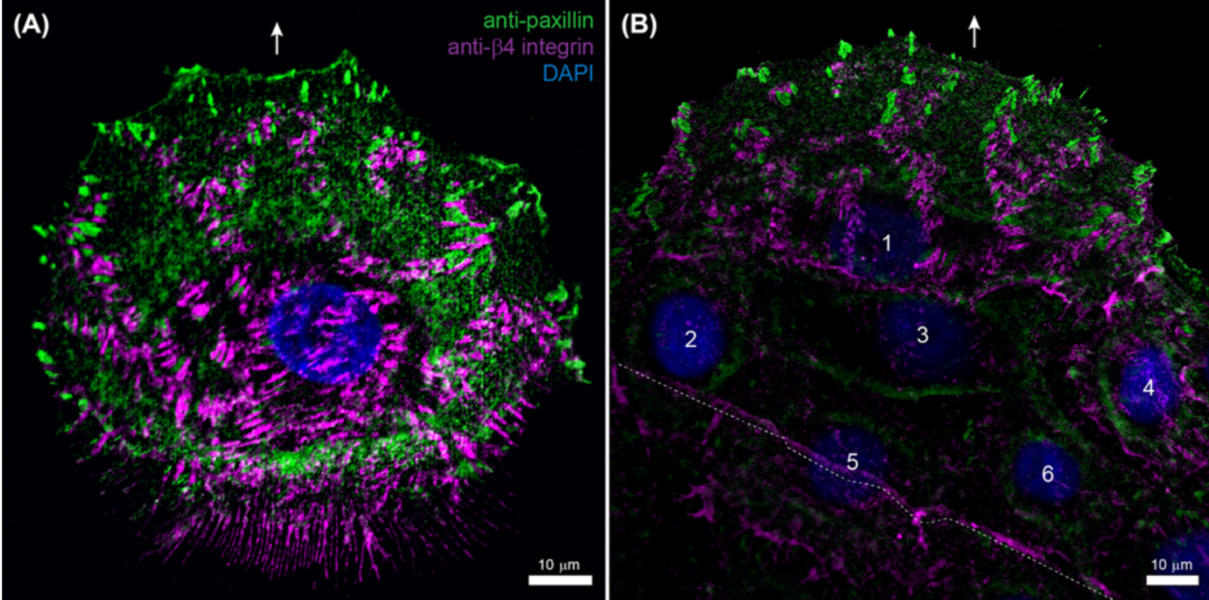

Figure 4. Cytoskeletal ECM anchorage sites generate unique superstructures in migrating keratinocytes
The images show projection views of fluorescence recorded in a single migrating primary human keratinocyte (**A**) and collectively migrating primary human epidermal keratinocytes (**B**) detecting the distribution of paxillin-labeled FAs and $\beta4$-integrin-labeled HD-LAs. The direction of migration is shown by arrows and the nuclei are demarcated in blue by DAPI staining. Note the presence of highly ordered arrays consisting of chevron-like hemidesmosomal adhesions with intercalated FAs in the single migrating keratinocyte in A and the leader cell (number 1) of the collectively migrating cell sheet (nuclei of followers numbered 2–6). The broken line shows the position of the barrier that was lifted to allow collective cell migration (B was adapted from Pora et al. [79]).

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What role does the KF–desmosome association play during cell migration?

Desmosomes are important for intercellular adhesion and tissue integrity (Figure 3; [87,88]). The crucial interplay of desmosomes and their associated KFs for epithelial tissue stability becomes apparent in keratinocytes lacking KFs. They present destabilized and smaller desmosomes due to elevated phosphorylation of the major KF–desmosome linker desmoplakin, which in turn renders epithelial sheets more sensitive to mechanical stress [89,90]. Conversely, loss of the desmosomal keratin-anchoring desmoplakin leads to compromised KF network organization in the epidermis with coincident reduction in mechanical tissue strength [62]. The observation that reversal of the p38 MAPK-mediated KF retraction in desmosomal autoimmune diseases restores tissue cohesion and stability [91,92] provides a hint to possible modes of regulating the dynamic keratin–desmosome interaction. Such regulatory mechanisms are crucial to allow epithelial cell migration. In the event of epidermal wound healing, the desmosome–KF complex undergoes highly regulated remodeling leading to reduced desmosomal adhesion [93]. In accordance, elevated desmosome turnover was observed in oral squamous cell carcinoma cells upon wounding [94]. Interestingly, this was coupled to reduced desmosome–KF co-localization and actin-dependent desmosome streaming which is in-line with recent reports on the interaction of desmosomal proteins with the actin cytoskeleton [58,95].

Desmosomal remodeling appears to be modulated by the specific keratin complement of each epithelial cell. The binding affinities of keratins to the major desmosomal linker desmoplakin are likely unique for each keratin [96,97]. Thus, re-expression of K5/K14 restored stable desmosomes in keratin-null keratinocytes, whereas K6/K17 rather induced destabilization of epithelial sheets via PKCα-mediated desmosome disassembly [98]. This result is in perfect agreement with the observation of elevated K6, K16 and K17 upon epidermal wounding and in hyperproliferative epidermis [38].

Desmosomes may play a central role in directed migration by preferential *de novo* formation at the extending front of moving cells and cell sheets. The mechanism may be similar to that observed in expanding epithelial cell colonies. They establish new desmosomal contacts at the periphery after adherens junctions are formed [99–102]. It has been further shown recently, that these nascent desmosomes serve as nucleation sites for KFs [99] as is the case during development of the keratin–desmosome scaffold in the trophoblast of murine blastocysts [103].

Obviously, desmosomes act as part of the overall mechanical adhesion system since weakening of desmosome–KF interaction disrupts not only cell–cell attachment but also cell–substrate adhesion and cell stiffness [104]. Similarly, absence of K6 accelerates cell migration by enhancing FA turnover and reducing desmoplakin [66].

Some of the most compelling evidence for a function of the interaction between keratins and cell junctions in cell movement comes from observations in the *Xenopus laevis* embryo [105,106]. In this system, KFs are linked to C cadherin-containing cell junctions. Pulling forces induce local KF recruitment thereby promoting directed migration by enhancing front-rear polarization and by preventing the formation of lateral protrusions through local Rac inhibition. Keratin reorganization was furthermore linked to 14-3-3 proteins.

How do keratins affect collective cell migration in wound healing?

Although many experiments have been performed *in vitro* on single migrating epithelial cells, one has to keep in mind that epithelial cells actually prefer collective migration *in vivo* [39]. In this situation, cells move as part of a contiguous sheet with a leader cell at the front generating most of the traction forces by the acto-myosin system linked to FAs. The resulting pulling forces are transmitted to the followers, which are in constant rearrangement [107]. Recent work on astrocytes has shown that their IF network comprising vimentin, glial fibrillary acidic protein and nestin controls the distribution of forces during collective migration [108]. The regulation involves plectin promoting actin-driven treadmilling of adherens junctions. Dynamics of FAs and their coupling to the acto-myosin system are also affected. The situation in epithelial cells may be somewhat different given the lack of direct association between keratins and FAs and, most importantly, the presence of desmosomes. Interestingly, the keratin complement of leader cells in epithelial sheets differs from that of follower cells [109,110]. Most likely, these filaments match the specific needs of leader cells in terms of cytoplasmic viscoelasticity and coupling to the ECM and neighboring cells.

Conclusions

Reports about the effect of keratins on the migratory phenotype differ vastly (selected examples in Table 2; [4,17,111]). Although the listed and other obvious discrepancies may be explained by technical flaws, use of different assay systems and the analysis of different parameters, they are so numerous that they likely point to context-dependent effects

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Table 2 Examples illustrating different consequences of inhibiting keratin polypeptide expression on the migratory phenotype

Keratin	Cell type (species)	Keratin alteration	Assay	Outcome	Reference
K8	Liver cancer (rat)	K8 shRNA	Scratch wounding	Decreased migration	[113]
K8	Breast cancer (human)	K8 overexpression	Scratch wounding	Decreased migration	[114]
		K8 shRNA		Increased migration	
K8	Colorectal cancer (human)	K8 shRNA	Scratch wounding	Decreased migration	[115]
K8	Gastric cancer (human)	K8 overexpression	Transwell migration	Increased migration	[116]
		K8 siRNA		Decreased migration	
K8/18	Endometrial cancer (human)	K8/K18 shRNA	Scratch wounding	Increased migration	[117]
K8/K18	Liver cancer(human)	K8/K18 shRNA	Scratch wounding	Increased migration	[117]
K18	Pancreatic cancer (human)	K18 siRNA	Random migration	Increased migration	[118]
K18	Lung cancer (human)	K18 shRNA	Scratch wounding Transwell migration	Decreased migration	[119]

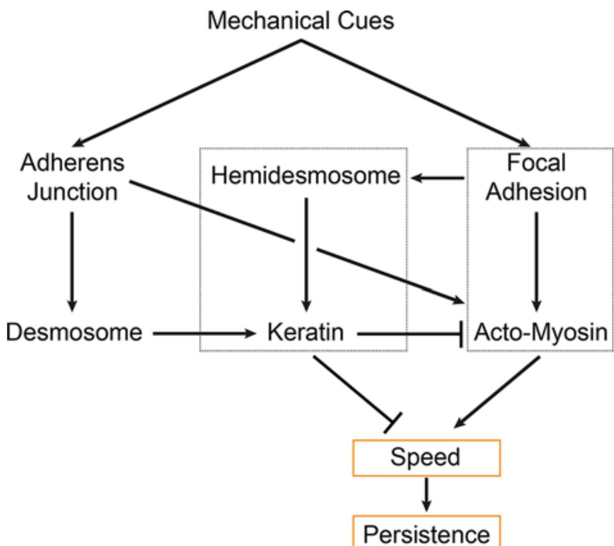

Figure 5. Simplified scheme illustrating key aspects of the cytoskeletal response to mechanical stimuli in migrating epithelial cells

Mechanical cues provided by the environment act primarily on FAs and adherens junctions, both of which activate the acto-myosin system as the major force-generating machinery. At the same time, FAs position HDs forming mutually dependent chevron patterns and adherens junctions facilitate the formation of desmosomes. HDs and desmosomes enhance the adhesion to the ECM and neighboring cells, respectively, and anchor the cytoplasmic keratin network. Together the keratin–HD/desmosome scaffold acts as a counterbalance to the FA/adherens junction-anchored acto-myosin system thereby reducing speed of migration but increasing persistence of migration.

of keratins relying on the precise keratin admixtures, the quantitative amounts of keratins and the specific microenvironment. We propose that each cell within a given epithelial tissue is characterized by a unique KF cytoskeleton determined by different combinations and amounts of the multiple keratin isoforms and their highly specific modification status reflecting cell cycle phase, functional state and position within the tissue. It is this property, which is at the base of tissue heterogeneity and the complex decision making for cellular migration.

The scheme depicted in Figure 5 summarizes how the keratin–HD/desmosome scaffold works together with the actin–FA/adherens junction system to achieve efficient directed cell migration in epithelial cells. In this review, we have focused on structural interaction of these systems, but acknowledge at the same time that they are intertwinded through multiple signaling pathways [112].

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Summary

- The migratory phenotype of a given epithelial cell is regulated by the specific KF complement and its post-translational modifications.
- The diversity of keratin polypeptides and their complex patterns of post-translational modifications make them ideally suited to fine-tune cytoplasmic viscoelasticity and mechanical coupling in response to mechanical signals.
- Keratins are part of a global mechanical scaffold that is dynamically linked to neighboring cells and the ECM by highly adhesive desmosomes and HDs, respectively.
- The keratin–HD/desmosome system provides a counterbalance to the force-generating actin–FA/adherens junction system to increase persistence of cell migration.

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Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

ECM, extracellular matrix; FA, focal adhesion; HD, hemidesmosome; HDLA, HD-like adhesion; IF, intermediate filament; KF, keratin intermediate filament; PAK1, P21 (RAC1) activated kinase 1; PKC, protein kinase C.

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