Available online at www.sciencedirect.com

ScienceDirect

ELSEVIER

Current Opinion in
Cell Biology

A keratin code defines the textile nature of epithelial tissue architecture

Jacopo Di Russo[1,2,3], Thomas M. Magin[4] and
Rudolf E. Leube[1]

Abstract

We suggest that the human body can be viewed as of textile nature whose fabric consists of interconnected fiber systems. These fiber systems form highly dynamic scaffolds, which respond to environmental changes at different temporal and spatial scales. This is especially relevant at sites where epithelia border on connective tissue regions that are exposed to dynamic microenvironments. We propose that the enormous heterogeneity and adaptability of epithelia are based on a "keratin code", which results from the cell-specific expression and posttranslational modification of keratin isotypes. It thereby defines unique cytoskeletal intermediate filament networks that are coupled across cells and to the correspondingly heterogeneous fibers of the underlying extracellular matrix. The resulting fabric confers unique local properties.

Addresses
[1] Institute of Molecular and Cellular Anatomy, RWTH Aachen University, Wendlingweg 2, 52074 Aachen, Germany
[2] Interdisciplinary Centre for Clinical Research, RWTH Aachen University, Pauwelstrasse 30, 52074 Aachen, Germany
[3] DWI - Leibniz-Institute for Interactive Materials, Forckenbeckstrasse 50, 52074 Aachen, Germany
[4] Institute of Biology, Division of Cell and Developmental Biology, Leipzig University, Philipp-Rosenthal-Str. 55, 04103 Leipzig, Germany

Corresponding author: Leube, Rudolf E. (rleube@ukaachen.de)

Introduction

Textiles are fiber-based materials created by weaving or knitting to produce porous, web-like structures. Products are not limited to clothing but are also found in wound dressings, different container types, houses, and even airplanes. Fiber texture,(i.e., mesh size, connectivity, and enclosed non-fibrous substances, confers unique properties on the respective materials. This manufacturing principle enhances stability while allowing lightweight design and can be coupled to specific functionalities such as defined viscoelasticity, breathability, thermoprotection, and degradability. Fiber-based (i.e., textile-like) materials are ubiquitous in the natural world. Biological fibers share many properties with fiber systems used in the technical world. They are long polymers with different degrees of deformability (bending, extension) and different dimensions (diameter) forming fabrics with defined mesh size and providing large surfaces that are functionalized (e.g., by specific binding sites). In contrast to their technical world counterparts, however, textile-like materials in the natural world can self-assemble and actively re-organize. Most importantly, they are responsive to mechanical and chemical cues guiding development and regeneration, serving as overall stress-protective systems, and causing pathology when defective. The concept of textile nature has been the basis of histology, which classifies tissues based on the unique arrangement of different cell types. While this overall concept has become somewhat outdated due to its focus on mere cellular composition, we want to revitalize it by reformulating its basic tenet. Using epithelia and their underlying extracellular matrix as an example, we will argue that tissue morphogenesis, cohesion, and function are facilitated by their unique and interconnected cytoskeletal intermediate filament (IF)-based fiber system in conjunction with the associated extracellular collagen-based fiber system (Figure 1). The resulting scaffolding exhibits astounding plasticity with tunability covering multiple length and time scales (Figure 2). It is the basis for the enormous structural and functional adaptability of epithelial tissues.

The keratin code defines epithelial fabric across multiple temporal and spatial scales

IFs are certainly the most complex of the three major cytoplasmic fiber systems that make up the cytoskeleton. In contrast to the actin-based microfilaments and the tubulin-based microtubules, IFs lack intrinsic polarity, are highly extensible and flexible, and form contiguous, interconnected transcellular networks in epithelia via desmosomal adhesions [1,2]. The epithelial keratin IF (KF) cytoskeleton is further diversified by

Figure 1
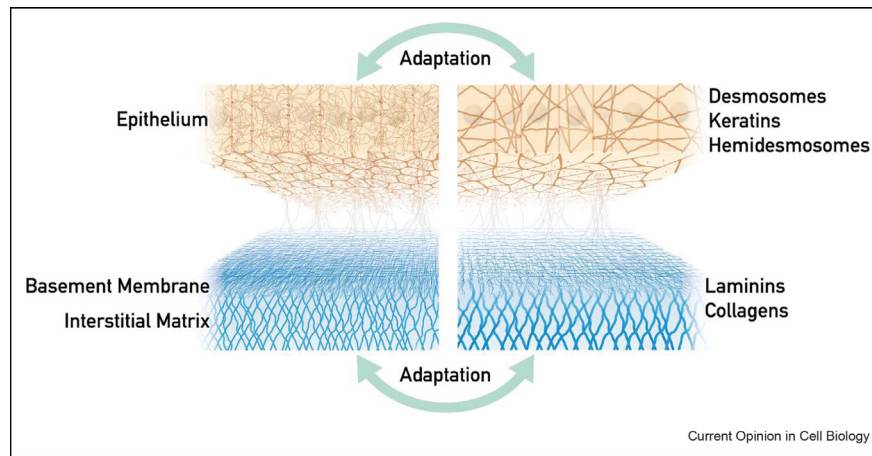
Schematic representation of the fiber systems forming transcellular scaffolds in interconnected epithelial cells that are connected to other types of fiber-based systems in the underlying extracellular matrix. The scheme provides an artificial view at the split interface between the epithelium on top and the extracellular matrix at the bottom. To emphasize their tight connectivity in situ, linking filamentous structures are indicated between both. The transcellular epithelial fiber scaffold encompasses the abundant keratin intermediate filaments that form 3D networks in the cytoplasm. They envelop and contact the nucleus and are connected to each other via desmosomal cell−cell adhesions. Anchorage to the extracellular matrix is mediated through hemidesmosomes, which bind via laminins to collagens. The extracellular matrix can be subdivided into the sheet-like basement membrane, which is in close apposition to the epithelium, and the more reticular interstitial matrix below, both of which can be distinguished by different collagens. The scheme further highlights that network morphology is subject to microenvironment-induced changes (compare left with right), which occur in a coordinated fashion in the physically linked epithelial and matrix fiber systems to adapt cell and tissue function.

the pairwise co-expression of 28 type I and 26 type II keratin polypeptides in humans and the mouse. They are expressed in cell type-, context- and function-dependent combinations [3,4]. It is generally accepted that each keratin polypeptide confers isotype-specific properties affecting assembly/disassembly kinetics, mechanical properties, and molecular interactions which are caused in part by isotype-specific posttranslational modifications [5,6]. We propose that the resulting diversity of IF cytoskeletons is fundamental for epithelial plasticity. The tunability of epithelial properties is thereby based on a "keratin code". It is defined by the

Figure 2
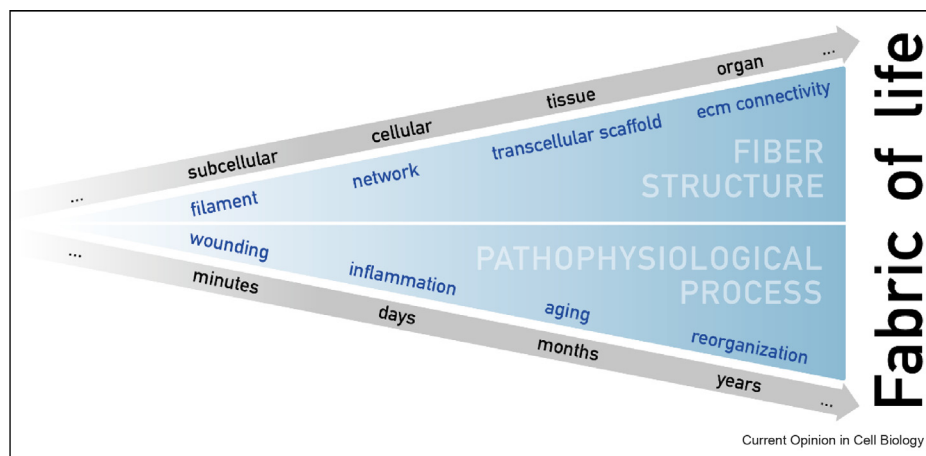
Length and time scales of fiber organization and dynamics. To understand the organization and functionality of the fiber-based fabric of life, different length and time scales must be considered. The scheme highlights the ranges most relevant for this review covering length scales from the subcellular to the organ level with the corresponding fiber-based structures and covering time scales from minutes to years with corresponding pathophysiological processes.

specific combination of keratin polypeptides and their unique posttranslational modification patterns at any point in time and any position within the cytoskeleton of a given epithelial cell. Figure 3 schematically exemplifies this type of keratin coding for properties and processes that are relevant for the epidermis. The fine-tuning of the local KF composition and modification produces an incredibly intricate and meticulously tailored fabric with spatially restricted unique functionalities. The selected examples taken from the recent literature serve to highlight aspects of the keratin code and its unique functionality.

An intriguing example of keratin isotype-specificity was recently described for the closely related type I keratins K14 and K15, which pair with the same type II keratins (typically K5) [7]. Airway basal cells respond to acute and chronic injury by switching from K15 to K14. A K14 knockout in airway basal cells inhibited their differentiation into ciliated adluminal cells but enhanced clonogenicity, whereas K15 knockout resulted in the opposite phenotype (i.e., impairment of clonogenicity but no interference with differentiation). They explained these opposing phenotypes by the isotype-specific association of K14 with the tumor suppressor stratifin/14-3-3σ. K14 knockout decreased stratifin leading to increased dNp63a oncogene expression. Büchau and colleagues [8] unveiled keratin isotype-specific regulation of hyperadhesion and desmosome composition. Hyperadhesion is facilitated by desmosomal cell—cell contacts, whereby they lose sensitivity to calcium depletion. Desmosomal hyperadhesion is not achieved in the absence of KFs. Expressing K14 in

keratin type I-deficient murine keratinocytes rescued hyperadhesion, expression of K17 did not. Upregulation of desmosomal proteins in the K17 background rescued the hyperadhesion capability, suggesting an involvement of keratin isotypes in the regulation of desmosomal constituents.

The large number of isotype-dependent posttranslationally modified sites has made it difficult to elucidate their distinct functions. This is especially true for phosphorylation affecting multiple and possibly interdependent sites in cell type- and subcellular region-specific patterns. Using murine keratinocytes lacking type II keratins has helped to unravel the importance of a major phosphorylation site in the head domain of K5 [9]. Phosphomimetic mutants prevented the formation of a KF network by interference with early assembly stages. Conversely, phosphorylation-deficient mutants formed KF networks with reduced turnover. Probably the best case made for the relevance of a single posttranslational modification was reported by Guo et al. [10]. By gene replacement, they introduced a mutation in the K14 gene substituting cysteine-encoding codon 373 with an alanine-encoding codon. As expected, the mutant polypeptide presented reduced disulfide bonding. Careful analysis linked this to enhanced proliferation, a faster epidermal transit time, and altered epidermal differentiation. These effects were mediated via a 14-3-3 signaling pathway resulting in aberrant subcellular partitioning of the mechanosensitive transcriptional regulator YAP1. Findings further indicated that cell mechanics were altered in the mutant background. The derived model predicts that disulfide bridge-dependent

Figure 3
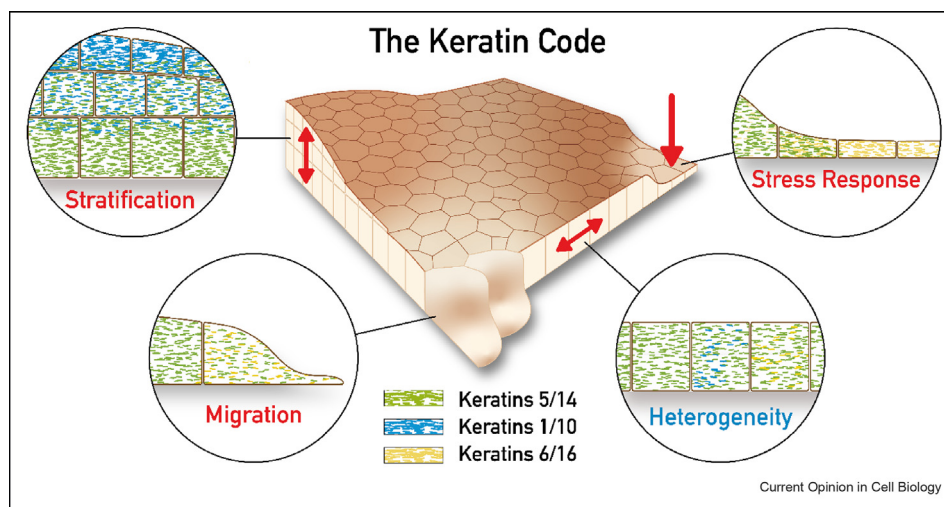
The keratin code. The scheme depicts different aspects of epithelial plasticity that are characterized by different combinations of keratin isotype expression (color code). The resulting cell- and differentiation-dependent expression of keratin isotypes, their abundance and posttranslational modifications (not shown) define the keratin code providing a unique identifier for a given epithelial cell in time and space. We hypothesize that the diverse range of epithelial functions such as stratification, migration and response to stress relies to a large extent on this keratin code, which is reflected by intra-epithelial heterogeneity.

KF network re-organization, which can occur during the transition from the basal to the suprabasal compartment, leads to perinuclear recruitment of 14-3-3σ and consecutive cytoplasmic YAP retention.

A major challenge in deciphering the keratin code and its functional relevance is the correlation of local heterogeneities in keratin composition and, more importantly, keratin modification with filament morphology (e.g., bundling, branching), protein–protein interaction (e.g., desmosomal/hemidesmosomal proteins, cytoskeletal cross-linkers, heat shock proteins, signaling proteins), and mechanical properties (e.g., viscoelasticity, stiffness). Evidence for such heterogeneities at the subcellular level was presented by Fois et al. [11], who detected increased keratin phosphorylation next to desmosomal adhesion sites. Similarly, keratin aggregates that are either induced by pathogenic keratin expression or by different types of stress are hyperphosphorylated [9,12]. It will be interesting to find out, to which degree and how posttranslational modification are involved in the association of keratins with the cytolinker plectin, which is known to affect keratin bundling and mesh size [13,14] with consequences for epithelial cell mechanics [15].

An important feature of the keratin code is its responsiveness to stimuli at very different time scales. An impressive example of a very rapid response was reported by Ratajczyk [16] who showed that association of KFs with the cytolinker epiplakin occurs within seconds (i.e., during fixation and in response to different stressors). The association is mediated by Ca^{++}-signaling and alters the dynamic properties of the keratin system. The more delayed responses occurring after wounding and during inflammation involve changes in keratin polypeptide synthesis. In the epidermis, these processes are coupled to the induction of K6, K16, and K17 ([3,5]; Figure 3). Permanent epithelial restructuring, which is characteristic for metaplasia, aging, and developmental processes is also associated with de novo expression of keratins (cf. [4]).

Desmosomal adhesion and actomyosin-dependent tension cooperate with the keratin code in defining local textile properties

The stratum-specific keratin polypeptide expression in the epidermis [4,17] suggests that the associated changes in filament type (single -> bundled -> aggregated) and filament distribution (cortical/radial -> pancytoplasmic -> cornified envelope) are major determinants of the changing basal to apical tissue texture. Another major factor is the changing force balance [18], which is believed to be driven by actomyosin-linked intercellular adherens junctions whereas the adaptation and resistance to mechanical forces are enabled by the

KF-desmosome system. Thus, it has been shown that the transition from cell–matrix to cell–cell adhesion is accompanied by the reorganization of the actin system from stress fibers to cortical actomyosin [19]. This process requires the polarity protein aPKC, since aPKC depletion results in the persistence of actin stress fibers in suprabasal cells. At the same time, the physiologically occurring KF re-distribution from the cortex to the cytoplasm is abrogated and KF bundling is increased highlighting the importance of actin-dependent pre-stress for suprabasal keratin network organization [19]. The work by Broussard et al. [20] further emphasized the contribution of the desmosome-keratin system in this process. They observed that uncoupling of desmosomes and KFs delayed stratification, while, unexpectedly, the expression of differentiation markers accelerated through precocious activation of the mechanosensitive transcriptional regulator serum response factor (SRF). They proposed that the keratin-desmosome connection acts as a clutch to support delamination of basal cells. In support, Thomas et al. [21] examined keratin-desmosome crosstalk during apoptotic cell extrusion in simple epithelial cell monolayers. They showed that desmosomes between remaining cells are transiently associated with actomyosin cables producing junctional tension to extrude the apoptotic cells.

The differences between the basal and suprabasal cytoskeleton are also reflected by differences in desmosome composition. The best-studied switch is that from the desmosomal cadherin desmoglein 3 in basal cells to desmoglein 1 in suprabasal cells. Even more, ectopic expression of desmoglein 1 in basal keratinocytes or in simple epithelial cells promotes stratification (cf. [22]). Mechanistically, desmoglein 1 redistributes molecular tension through rearrangement of cortical F-actin via Arp1/3-dependent actin polymerization [23]. Collectively, one can conclude that the keratin cytoskeleton provides a multifunctional matrix that is tightly integrated across cell borders through desmosomes forming a contiguous transcellular network with stratum-specific properties in the epidermis, whose architecture adapts to the local force balance via mechanosensing. The resulting fabric is highly adaptable and integrates metabolic functions [24].

The epithelial and extracellular fiber systems are mechanically and functionally connected

The fabric of the epithelial fiber systems differs profoundly from that of the underlying extracellular matrix (ECM). But both are physically linked via hemidesmosomes, which have been classified as compositionally distinct type 1 in stratified and pseudostratified epithelia and type 2 in simple epithelia. Both types are attached to the basement membrane by binding to

trimeric laminins, which form reticular sheets and are, in turn, attached to the collagen type IV network. Integrin α6β4 and the bullous pemphigoid antigen BP180 of type 1 hemidesmosomes interact with laminin 332 [25]. Type 2 hemidesmosomes can also interact with α5-containing laminins (i.e., laminins 511 and 521) [26].

Conditional removal of laminin 332 provided compelling evidence for the fundamental role of type 1 hemidesmosomes in the maintenance of epidermal homeostasis in the adult skin [27]. It induced epidermal thickening and increased desquamation as a consequence of a modified differentiation program of basal keratinocytes. This was reflected by major changes in keratin expression (i.e., increased synthesis of K6a, K6b, and K16) and by increased cornified envelope proteins and cellular stress markers. Furthermore, disorganization of the actin cytoskeleton and cell shape were readily apparent.

In a similar vein, the laminin α5 chain has been shown to regulate keratin expression and the differentiation state in mammary epithelium [28]. Binding of K5/K14-positive basal cells to laminin α5 induces their differentiation into K8/K18-positive luminal cells, requiring β4 integrin and further downstream signaling. These findings are in line with a study on mammary cancer-derived epithelial acini [29] showing that their malignant transformation occurs only in the absence of a tight hemidesmosomal connection between the ECM and the keratin network. It further demonstrated that the lack of hemidesmosomal integrin clustering is regulated by a complex interplay between matrix stiffness and laminin density. While low matrix stiffness allows clustering, stiff matrix prevents it and can be rescued by increasing laminin density.

It is becoming increasingly evident that cell–cell and cell-ECM adhesion together with mechanical feedback cycles regulate epithelial function and mechanical homeostasis (cf. [30]). Mechanical homeostasis relies on the dynamic equilibrium of tensile forces transmitted between neighboring cells and the ECM. This equilibrium is based on the active regulation of the cytoskeleton and its associated junctions, which impact gene expression through their connection to the nucleus [31]. Fujiwara et al. reported that keratin networks regulate mechanotransduction through a Rho signaling pathway upstream of cell-ECM adhesion formation and organized cell migration, a pathway relevant to the pathogenesis of Epidermolysis bullosa simplex [32]. Recent data further indicate that the 3D organization of the keratin network is guided by cues from the ECM [33,34]. Sensing ECM rigidity is facilitated by crosstalk between the keratin and the actin cytoskeleton. Laly et al. [35] demonstrated that the K14 network adapts to ECM stiffening in an F-actin-dependent fashion by becoming more bundled and rigid. Further evidence for the pivotal keratin-actin crosstalk in the mechanotransduction of ECM rigidity was provided by Wang et al. [36], who reported that keratinocytes lacking integrin α6β4 exert reduced traction force and implicated the cytoskeletal linker plectin in this process. It has been proposed that plectin is involved in the F-actin-dependent organization of the keratin network into a circumferential subcortical rim and the radial keratin spokes both of which are attached to desmosomal adhesion sites [15,35,37]. Genetic removal of plectin resulted in the loss of the circumferential rim and increased mechanical fragility of cell sheets [15].

The keratin-actin crosstalk also plays an important role in epithelial cell migration on different matrix types. While actin together with focal adhesions has an exploratory probing function testing ECM stiffness and composition, keratins follow the actin system and fulfill a stabilizing function. The observed inward-directed keratin flow is always slower than the retrograde actin flow [38]. Coordination of both allows efficient directed migration. Keratins therefore provide a templating function: They reduce the speed of migration but increase its persistence [38,39]. In the presence of laminin 332 hemidesmosomes are preferentially formed at the leading front of migrating primary keratinocytes generating characteristic chevron-like structures [40]. These chevrons are laterally flanked by focal adhesions. Together, they are subject to treadmilling: Focal adhesions appear first at the leading edge. Hemidesmosomal chevrons subsequently form between paired focal adhesions. They extend ribbons of focal adhesion-flanked chevrons which serve to translocate the cell body forward. At the cell rear, focal adhesions and hemidesmosomal chevrons disassemble in reverse order. This arrangement was detected most prominently in leading cells of collectively migrating cell sheets [40].

In addition to the hemidesmosome-mediated direct association of epithelial cells to the basement membrane, the interstitial matrix underneath is also integrated into the pervasive and interactive scaffold that we refer to as the fabric of life. In some epithelia, such as the cornea and skin, collagen type VII hooks onto the fibrillar collagens type I and III of the interstitial matrix and binds collagen type IV and laminin 332 in the basement membrane forming structures referred to as anchor fibrils [41,42]. Interestingly, interstitial matrix changes impact basement membrane thickness and stiffness in the skin [43]. These changes lead to a reduction of chromatin accessibility in the stem cells of hair follicles resulting in progressively reduced regeneration potential [44].

We are currently far away from a complete understanding of subepithelial ECM heterogeneity, although

several efforts are underway to systematically explore its biochemical diversity in relation to topology and function at different interfaces [45,46].

Future perspectives and challenges

A comprehensive view of the interconnected fiber systems of the human body is needed to understand tissue morphogenesis, remodeling, and malformation as fundamental determinants of functional tissue differentiation, homeostasis, and malfunction, respectively. It requires multimodal measurements of morphological features, their biochemical composition, and mechanical properties. These analyses are needed at different lengths and time scales to understand emergent features of the keratin code and its impact on the functionality of the epithelial fabric (Figure 2). To detect the underlying mechanisms, tools have to be refined and adjusted for the examination of filaments at the subcellular level, networks at the cellular level, transcellular scaffolds at the epithelial tissue level, and their connection to the ECM fiber systems at the organ level. The analyses will help to understand acute responses occurring after wounding and in various acute stress situations, chronic responses that are induced, for example, during inflammation, and long-lasting permanent responses that take place during development, chronic stress, and aging.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

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

   * of special interest
   ** of outstanding interest

1. Block J, Schroeder V, Pawelzyk P, Willenbacher N, Koster S: **Physical properties of cytoplasmic intermediate filaments**. *Biochim Biophys Acta* 2015, **1853**:3053–3064.

2. Hatzfeld M, Keil R, Magin TM: **Desmosomes and intermediate filaments: their consequences for tissue mechanics**. *Cold Spring Harbor Perspect Biol* 2017, **9**.

3. Jacob JT, Coulombe PA, Kwan R, Omary MB: **Types I and II keratin intermediate filaments**. *Cold Spring Harbor Perspect Biol* 2018, **10**.

4. Moll R, Divo M, Langbein L: **The human keratins: biology and pathology**. *Histochem Cell Biol* 2008, **129**:705–733.

5. Redmond CJ, Coulombe PA: **Intermediate filaments as effectors of differentiation**. *Curr Opin Cell Biol* 2021, **68**:155–162.

6. Snider NT, Omary MB: **Post-translational modifications of intermediate filament proteins: mechanisms and functions**. *Nat Rev Mol Cell Biol* 2014, **15**:163–177.

7. Ievlev V, Lynch TJ, Freischlag KW, Gries CB, Shah A,
** Pai AC, Ahlers BA, Park S, Engelhardt JF, Parekh KR: **Krt14 and Krt15 differentially regulate regenerative properties and differentiation potential of airway basal cells**. *JCI Insight* 2023:8.
This work unveils unexpected and fundamentally opposing effects of the related keratins 14 and 15 on differentiation and proliferation of airway basal cells. The effects are linked to isotype-specific pathway activation involving 14-3-3σ.

8. Buchau F, Vielmuth F, Waschke J, Magin TM: **Bidirectional
** regulation of desmosome hyperadhesion by keratin isotypes and desmosomal components**. *Cell Mol Life Sci* 2022, **79**:223.
The study addresses keratin isotype-specific regulation of desmosomal adhesion. While re-expression of keratin 14 in keratin type I-deficient keratinocytes restores desmosomal hyperadhesion, re-expression of keratin 17 does not.

9. Sawant M, Schwarz N, Windoffer R, Magin TM, Krieger J, Mucke N, Obara B, Jankowski V, Jankowski J, Wally V, et al.: **Threonine 150 phosphorylation of keratin 5 is linked to Epidermolysis bullosa simplex and regulates filament assembly and cell viability**. *J Invest Dermatol* 2018, **138**: 627–636.

10. Guo Y, Redmond CJ, Leacock KA, Brovkina MV, Ji S, Jaskula-Ranga V, Coulombe PA: **Keratin 14-dependent disulfides regulate epidermal homeostasis and barrier function via 14-3-3sigma and YAP1**. *Elife* 2020, **9**.

11. Fois G, Weimer M, Busch T, Felder ET, Oswald F, von Wichert G, Seufferlein T, Dietl P, Felder E: **Effects of keratin phosphorylation on the mechanical properties of keratin filaments in living cells**. *Faseb J* 2013, **27**:1322–1329.

12. Woll S, Windoffer R, Leube RE: **p38 MAPK-dependent shaping of the keratin cytoskeleton in cultured cells**. *J Cell Biol* 2007, **177**:795–807.

13. Moch M, Windoffer R, Schwarz N, Pohl R, Omenzetter A, Schnakenberg U, Herb F, Chaisaowong K, Merhof D, Ramms L, et al.: **Effects of plectin depletion on keratin network dynamics and organization**. *PLoS One* 2016, **11**, e0149106.

14. Osmanagic-Myers S, Gregor M, Walko G, Burgstaller G, Reipert S, Wiche G: **Plectin-controlled keratin cytoarchitecture affects MAP kinases involved in cellular stress response and migration**. *J Cell Biol* 2006, **174**:557–568.

15. Prechova M, Adamova Z, Schweizer AL, Maninova M, Bauer A,
** Kah D, Meier-Menches SM, Wiche G, Fabry B, Gregor M: **Plectin-mediated cytoskeletal crosstalk controls cell tension and cohesion in epithelial sheets**. *J Cell Biol* 2022:221.
The work examines the role of plectin in mechanical homeostasis of epithelial sheets uncovering the role of the keratin-desmosome scaffold in a feedback cycle with the actin cytoskeleton.

16. Ratajczyk S, Drexler C, Windoffer R, Leube RE, Fuchs P:
** **A Ca(2+)-mediated switch of epiplakin from a Diffuse to keratin-bound state affects keratin dynamics**. *Cells* 2022:11.
The authors report, that the plakin family member epiplakin binds rapidly to keratin filaments in situations of ER-, oxidative and UV-stress and even during cell fixation. They showed that this response depended on elevated cytoplasmic Ca^{2+} levels and resulted in increased stability of the keratin filament network.

17. Li J, Ma J, Zhang Q, Gong H, Gao D, Wang Y, Li B, Li X, Zheng H, Wu Z, *et al.*: **Spatially resolved proteomic map shows that extracellular matrix regulates epidermal growth**. *Nat Commun* 2022, **13**:4012.

18. Miroshnikova YA, Le HQ, Schneider D, Thalheim T, Rubsam M,
** **Bremicker N, Polleux J, Kamprad N, Tarantola M, Wang I, *et al.*: Adhesion forces and cortical tension couple cell proliferation and differentiation to drive epidermal stratification**. *Nat Cell Biol* 2018, **20**:69−80.

19. Rubsam M, Pullen R, Tellkamp F, Bianco A, Peskoller M,
* Bloch W, Green KJ, Merkel R, Hoffmann B, Wickstrom SA, *et al.*: **Polarity signaling balances epithelial contractility and mechanical resistance**. *Sci Rep* 2023, **13**:7743.
The study examines the relationship between actomyosin contractility and keratin network organization during stratification and how this crosstalk may be involved in mechanical resilience. They show that the transition in cytoskeletal network organization is regulated by aPKC.

20. Broussard JA, Koetsier JL, Hegazy M, Green KJ: **Desmosomes
** **polarize and integrate chemical and mechanical signaling to govern epidermal tissue form and function**. *Curr Biol* 2021, **31**: 3275−3291 e3275.
The study provides evidence that the desmosome-keratin system acts as clutch to support the basal cell delamination during epidermal stratification and show that it is inversely linked to regulation of epidermal differentiation.

21. Thomas M, Ladoux B, Toyama Y: **Desmosomal junctions govern tissue integrity and actomyosin contractility in apoptotic cell extrusion**. *Curr Biol* 2020, **30**:682−690 e685.

22. Hegazy M, Perl AL, Svoboda SA, Green KJ: **Desmosomal cadherins in health and disease**. *Annu Rev Pathol* 2022, **17**: 47−72.

23. Nekrasova O, Harmon RM, Broussard JA, Koetsier JL, Godsel LM, Fitz GN, Gardel ML, Green KJ: **Desmosomal cadherin association with Tctex-1 and cortactin-Arp2/3 drives perijunctional actin polymerization to promote keratinocyte delamination**. *Nat Commun* 2018, **9**:1053.

24. Hegazy M, Koetsier JL, Huffine AL, Broussard JA, Godsel BM, Cohen-Barak E, Sprecher E, Wolfgeher DJ, Kron SJ, Godsel LM, *et al.*: **Epidermal stratification requires retromer-mediated desmoglein-1 recycling**. *Dev Cell* 2022, **57**: 2683−2698. e2688.

25. Sugawara K, Tsuruta D, Ishii M, Jones JC, Kobayashi H: **Laminin-332 and -511 in skin**. *Exp Dermatol* 2008, **17**:473−480.

26. Kikkawa Y, Sanzen N, Fujiwara H, Sonnenberg A, Sekiguchi K: **Integrin binding specificity of laminin-10/11: laminin-10/11 are recognized by alpha 3 beta 1, alpha 6 beta 1 and alpha 6 beta 4 integrins**. *J Cell Sci* 2000, **113**(Pt 5):869−876.

27. Tayem R, Niemann C, Pesch M, Morgner J, Niessen CM,
* Wickstrom SA, Aumailley M: **Laminin 332 is indispensable for homeostatic epidermal differentiation programs**. *J Invest Dermatol* 2021, **141**:2602−2610. e2603.
This is an important study showing the critical role of laminin 332 in maintaining basal keratinocyte homeostasis in the adult epidermis. The genetic removal of laminin 332 in adult mice induces basal keratinocytes to upregulate the expression of differentiation genes, including keratin 6a, 6b and 16 and cytoskeleton-associated proteins such as filamin b, desmoplakin, and palladin.

28. Englund JI, Bui H, Dinc DD, Paavolainen O, McKenna T,
* Laitinen S, Munne P, Klefstrom J, Peuhu E, Katajisto P: **Laminin matrix adhesion regulates basal mammary epithelial cell identity**. *J Cell Sci* 2022:135.
The work presents a nice example of how basement membrane laminins defines basal cell identity and keratin expression via β4 integrin signaling.

29. Chaudhuri O, Koshy ST, Branco da Cunha C, Shin JW, Verbeke CS, Allison KH, Mooney DJ: **Extracellular matrix stiffness and composition jointly regulate the induction of malignant phenotypes in mammary epithelium**. *Nat Mater* 2014, **13**:970−978.

30. Kozyrina AN, Piskova T, Di Russo J: **Mechanobiology of epithelia from the perspective of extracellular matrix heterogeneity**. *Front Bioeng Biotechnol* 2020, **8**:596599.

31. Iskratsch T, Wolfenson H, Sheetz MP: **Appreciating force and shape-the rise of mechanotransduction in cell biology**. *Nat Rev Mol Cell Biol* 2014, **15**:825−833.

32. Fujiwara S, Deguchi S, Magin TM: **Disease-associated keratin mutations reduce traction forces and compromise adhesion and collective migration**. *J Cell Sci* 2020, **133**. jcs243956.

33. Windoffer R, Schwarz N, Yoon S, Piskova T, Scholkemper M,
* Stegmaier J, Bonsch A, Di Russo J, Leube RE: **Quantitative mapping of keratin networks in 3D**. *Elife* 2022:11.
The study describes the full 3D segmentation of epithelial keratin filament networks allowing quantitative assessment and of network properties at subcellular resolution.

34. Yoon S, Windoffer R, Kozyrina AN, Piskova T, Di Russo J,
* Leube RE: **Combining image restoration and traction force microscopy to study extracellular matrix-dependent keratin filament network plasticity**. *Front Cell Dev Biol* 2022, **10**: 901038.
The study presents workflows for multimodal monitoring of epithelial cells to examine how the extracellular matrix and wounding affect the epithelial force balance and keratin network dynamics.

35. Laly AC, Sliogeryte K, Pundel OJ, Ross R, Keeling MC,
** **Avisetti D, Waseem A, Gavara N, Connelly JT: **The keratin network of intermediate filaments regulates keratinocyte rigidity sensing and nuclear mechanotransduction**. *Sci Adv* 2021, **7**.
This key study demonstrates the keratin cytoskeleton as pivotal in cell mechanosensation. The data show that extracellular matrix stiffness affects the organization of the keratin 14 network, nuclear lamina, and heterochromatin remodeling. The crosstalk between the keratin and actin cytoskeleton regulates this mechanosensation.

36. Wang W, Zuidema A, Te Molder L, Nahidiazar L, Hoekman L, Schmidt T, Coppola S, Sonnenberg A: **Hemidesmosomes modulate force generation via focal adhesions**. *J Cell Biol* 2020:219.

37. Quinlan RA, Schwarz N, Windoffer R, Richardson C, Hawkins T, Broussard JA, Green KJ, Leube RE: **A rim-and-spoke hypothesis to explain the biomechanical roles for cytoplasmic intermediate filament networks**. *J Cell Sci* 2017, **130**: 3437−3445.

38. Pora A, Yoon S, Dreissen G, Hoffmann B, Merkel R, Windoffer R, Leube RE: **Regulation of keratin network dynamics by the mechanical properties of the environment in migrating cells**. *Sci Rep* 2020, **10**:4574.

39. Seltmann K, Roth W, Kroger C, Loschke F, Lederer M, Huttelmaier S, Magin TM: **Keratins mediate localization of hemidesmosomes and repress cell motility**. *J Invest Dermatol* 2013, **133**:181−190.

40. Pora A, Yoon S, Windoffer R, Leube RE: **Hemidesmosomes and focal adhesions treadmill as separate but linked entities during keratinocyte migration**. *J Invest Dermatol* 2019, **139**: 1876−1888 e1874.

41. Brittingham R, Uitto J, Fertala A: **High-affinity binding of the NC1 domain of collagen VII to laminin 5 and collagen IV**. *Biochem Biophys Res Commun* 2006, **343**:692−699.

42. Keene DR, Sakai LY, Lunstrum GP, Morris NP, Burgeson RE: **Type VII collagen forms an extended network of anchoring fibrils**. *J Cell Biol* 1987, **104**:611−621.

43. Koester J, Miroshnikova YA, Ghatak S, Chacon-Martinez CA, Morgner J, Li X, Atanassov I, Altmuller J, Birk DE, Koch M, *et al.*: **Niche stiffening compromises hair follicle stem cell potential during ageing by reducing bivalent promoter accessibility**. *Nat Cell Biol* 2021, **23**:771–781.

44. Persa OD, Koester J, Niessen CM: **Regulation of cell polarity and tissue architecture in epidermal aging and cancer**. *J Invest Dermatol* 2021, **141**:1017–1023.

45. Naba A: **Ten years of extracellular matrix proteomics: accomplishments, challenges, and future perspectives**. *Mol Cell Proteomics* 2023, **22**:100528.

46. Tsutsui K, Machida H, Nakagawa A, Ahn K, Morita R, Sekiguchi K, Miner JH, Fujiwara H: **Mapping the molecular and structural specialization of the skin basement membrane for inter-tissue interactions**. *Nat Commun* 2021, **12**:2577.