Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

Plasticity of cytoplasmic intermediate filament architecture determines cellular functions

Nicole Schwarz and Rudolf E. Leube

Abstract

Cytoplasmic intermediate filaments endow cells with mechanical stability. They are subject to changes in morphology and composition if needed. This remodeling encompasses entire cells but can also be restricted to specific intracellular regions. Intermediate filaments thereby support spatially and temporally defined cell type-specific functions. This review focuses on recent advances in our understanding of how intermediate filament dynamics affect the underlying regulatory pathways. We will elaborate on the role of intermediate filaments for the formation and maintenance of surface specializations, cell migration, contractility, organelle positioning, nucleus protection, stress responses and axonal conduction velocity. Together, the selected examples highlight the modulatory role of intermediate filament plasticity for multiple cellular functions.

Addresses

Institute of Molecular and Cellular Anatomy, RWTH Aachen University, Wendlingweg 2, 52074 Aachen, Germany

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

Current Opinion in Cell Biology 2023, **85:**102270

This review comes from a themed issue on **Cell Dynamics (2023)**

Edited by **Kandice Tanner** and **Anne Straube**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.ceb.2023.102270

Introduction

Intermediate filaments are major components of the cytoskeleton. They are composed of a diverse group of polypeptides with more than 70 members. Based on their gene structure, sequence homologies, and assembly characteristics they are grouped into 6 types with cell type-specific expression patterns (Table 1). The intermediate filament polypeptides share a common tripartite structure consisting of a defined central rod and highly divergent, polypeptide-specific head and tail domains. The α-helical rod domains pair with each other and self-assemble subsequently via consecutive intermediates into ∼10 nm filaments, which bundle, branch and form complex 3D networks. Unlike actin filaments and microtubules, intermediate filaments are non-polar, highly flexible, and are able to withstand high mechanical stresses. The intermediate filament cytoskeleton preserves not only the mechanical integrity of cells but also supports many other cellular processes including organelle function and positioning, directed migration, metabolism and stress responses (e.g., Refs. [1,2]).

The different functions are linked to unique intermediate filament network compositions and arrangements. This requires stability on the one hand but also remodeling on the other hand to adjust to the respective cell type- and differentiation-dependent local functions. The necessary dynamic filament and network architectures are achieved by interlaced processes, notably (Figure 1):

i) controlled cycles of assembly and disassembly: Assembly of intermediate filaments (nucleation, elongation, branching, bundling) is counterbalanced by filament disassembly at homeostasis. Shifting the equilibrium by either increasing assembly or disassembly allows rapid remodeling without the need of protein biosynthesis.

ii) local turnover: Two mechanisms govern local filament turnover. First, lateral subunit exchange can occur throughout the network albeit at different rates. Mechanistically, this is achieved by release and recruitment of soluble subunits resulting in heterogeneity of filament diameter. Second, filament severing allows excision or insertion of filamentous particles resulting in filament shortening and elongation, respectively.

iii) filament modification: Filament modification is achieved by interaction with proteinaceous regulators and posttranslational modification. Intermediate filament-associated proteins modulate the morphology and spatial arrangement of intermediate filaments and their turnover resulting in cell type-specific arrangements with specific dynamic properties. Posttranslational modifications fine-tune network morphology, dynamics and function at subcellular precision and multi-scale temporal resolution.

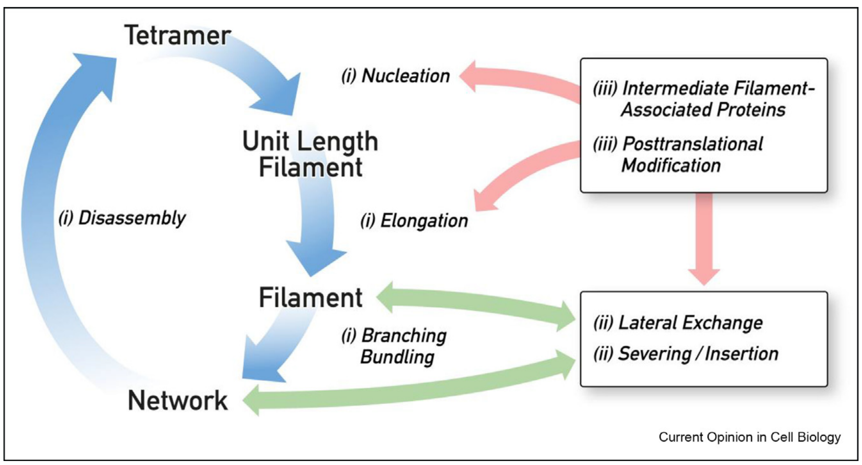
The regulation and kinetics of the listed mechanisms are specific for each intermediate filament polypeptide type. The resulting range of network

Table 1

List of intermediate filament polypeptides. The intermediate filament protein families are grouped into types I-VI with distinct distribution patterns.

Type	Members	Distribution
I	'Acidic' keratins	Epithelial cells
II	'Basic' keratins	Epithelial cells
III	Vimentin	Mesenchymal cells
	Desmin, Syncoilin	Muscle cells
	Glial fibrillary acidic protein (GFAP)	Glial cells
	Peripherin	Neurons
IV	Neurofilament proteins (NF-L, NF-M, NF-H), α-Internexin	Neurons
	Synemin	Astrocytes, muscle cells
	Nestin	Developing and regenerating cells
V	Lamins	Nuclear lamina of all nucleated cells
VI	Filensin, Phakinin	Lens fiber cells

Figure 1



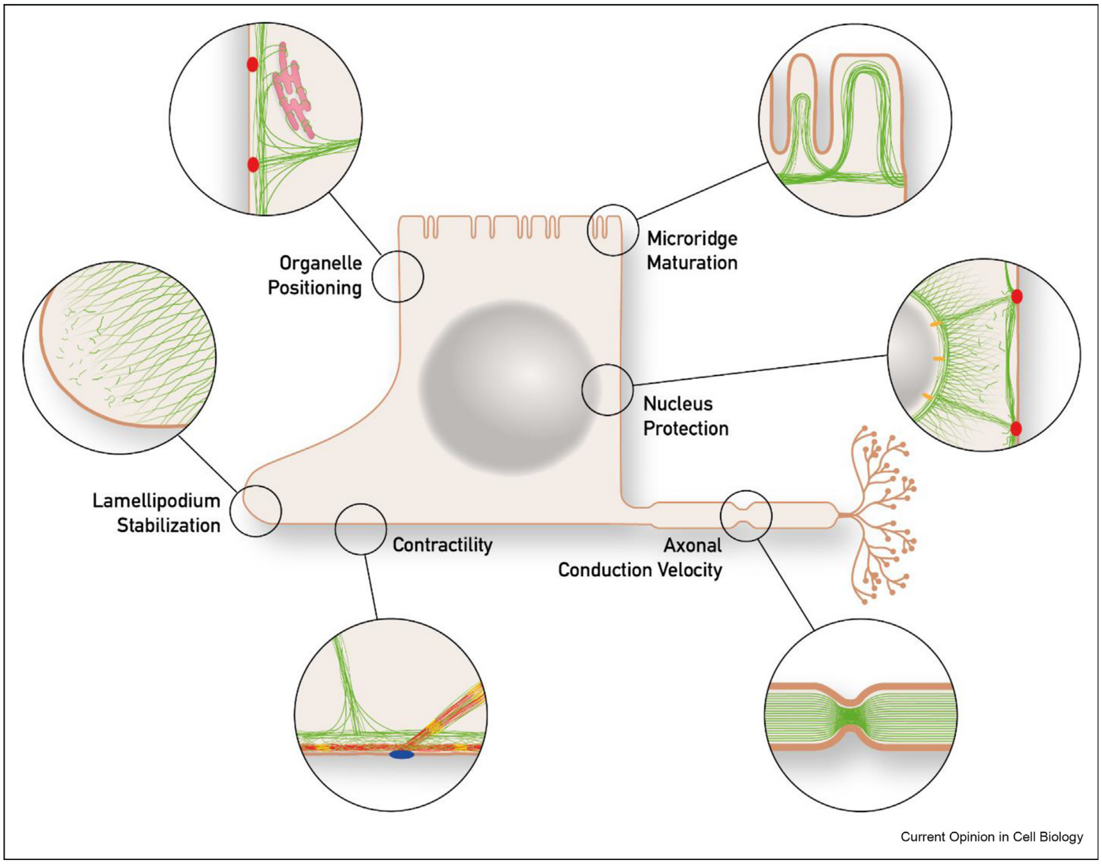
The scheme illustrates how a dynamic intermediate filament network architecture is achieved. Intermediate filament networks undergo a constant cycle of assembly (nucleation, elongation, branching and bundling) and disassembly. Filaments are modified locally by severing and insertion as well as lateral exchange of subunits. Binding of intermediate filament-associated proteins and posttranslational modifications control and fine-tune these processes.

plasticity facilitates cell type-specific compartmentalization for localizing functions in dedicated niches. For this review, we selected examples from the last two years which focus on advances in the understanding of how the morphology and dynamics of cytoplasmic intermediate filaments affect cellular functions (Figure 2).

Intermediate filament assembly supports subcellular domain specification

Nucleation is the assembly of filaments from soluble oligomeric subunits, i.e. dimers or tetramers. While nucleation of intermediate filaments occurs in vitro without the addition of nucleoside triphosphates or proteinaceous factors, its in vivo regulation is poorly understood. Evidence for controlled nucleation in living cells has been obtained through time-lapse recordings of fluorescently labelled intermediate filament polypeptides detecting the appearance of small particles in certain cellular subdomains [3–6]. It does not rely on de novo protein synthesis but re-uses soluble intermediate filament subunits [7]. In the case of vimentin and keratin, nucleating particles were most frequently observed in the cell periphery [3,8]. It has been suggested that focal adhesions serve as important regulators of vimentin nucleation acting either through direct physical binding or signaling [9,10]. Nucleation of keratin filament precursors has been documented next to nascent hemidesmosomes and desmosomes that appear in the periphery of growing epithelial cell colonies [11,12]. More importantly, keratin filament nucleation was also recorded in developing murine blastocysts at a time, when the first cytoplasmic

Figure 2



The scheme highlights examples that illustrate how distinct, cell type-specific intermediate filament network configurations support local cellular processes. Thus, unique intermediate filament network morphologies protect the nucleus, are involved in microridge formation and maturation, help to position organelles, stabilize lamellipodia, affect cellular contractility and influence axonal conduction velocity.

intermediate filament network is generated [11]. A potential nucleating factor is Ndel1, which was recently shown to promote keratin assembly near desmosomes [13].

The nucleated particles elongate and integrate into the pre-existing intermediate filament networks as has been well documented for keratins, vimentin and neurofilament polypeptides [8,14]. These particles are highly motile and are transported in a microtubule and actin filament dependent fashion until they are integrated into the network. The overall net effect is that network architecture is non-polarized, when nucleation occurs without direcctional preference. This is the case in cells that are exposed to the same environment on all sides, e.g., in suprabasal cells of the epidermis that are completely surrounded by and bound to similar neighboring suprabasal cells. If nucleation occurs only in certain peripheral regions, which are defined, for example, by restricted contacts to neighboring cells or the extracellular matrix, it will lead to asymmetric, i.e., polarized network remodeling.

Intermediate filaments affect cellular contractility

A consequence of differential assembly is the generation of cell type-specific network topologies. Among them, the rim-and-spokes model has received increasing attention [11,15–17]. It describes keratin intermediate filament networks in confluent epithelial cells consisting of a layer of filaments below the plasma membrane, i.e., the circumferential rim interconnecting desmosomes, and radial filament bundles, i.e., the spokes that connect desmosomes to stable filaments forming the perinuclear cage [16]. The keratin rim is adjacent to the submembraneous actin cortex. It may be physically attached to it via the cytolinker plectin. In accordance, plectin knock-out hinders the integration of cortical actin and keratin and consequently results in loss of the keratin rim, which leads to an increase of F-actin stress fibers [17].

Even more, vimentin intermediate filaments and F-actin form interpenetrating networks [18]. An interesting study reported on the interdependency of cortical actin and vimentin. Treating cells with electrophiles led to a reduction of cortical vimentin and redistribution of cortical actin into actin stress fibers. When cells produced vimentin mutants with a reduced sensitivity to electrophiles, vimentin redistribution was less affected and actin stress fiber formation was prevented [19].

Another example of intermediate filament-actin interdependency was recently described in smooth muscle cells. These cells co-express nestin and vimentin, which form heteropolymers. Increased contractility went along with increased recruitment of polo-like kinase 1 (Plk1) to nestin leading to activation of Plk1 and phosphorylation of nestin and vimentin. Vimentin phosphorylation presumably releases vimentin from the cortex resulting in increased plasma membrane localization of the actin-regulatory proteins cortactin and profilin. Cortactin and profilin are known to promote F-actin stress fiber formation and cell contractibility. In accordance, downregulation of nestin led to a reduced activation of Plk1 and reduced F-actin stress fiber formation and cell contractibility [20]. This nicely fits with the observation that vimentin knock-out cells are less contractile [21].

Intermediate filaments contribute to the formation and stabilization of cellular protrusions

Dynamic membrane protrusions such as microvilli and cilia rely on juxtamembraneous actin filament- and microtubule-based-scaffolds [22,23]. The role of intermediate filaments in these structures is more restricted and mostly relevant for their maintenance and stabilization. They may serve as a flexible, yet resilient counter bearing between the rather rigid brush border/ciliated surface and the comparatively soft cytoplasm. Viscoelasticity mapping of this interface in the intestinal brush border of *C. elegans* by Brillouin microscopy confirmed this notion [24]. Recent publications furthermore emphasized the role of keratin intermediate filaments in the formation and maintenance of microridges [25–27]. Microridges are rigid, actin-based apical surface protrusions that have been described in zebrafish epiderm cells but also occur in multiple human epithelia. The interaction of keratins with the plakin family members periplakin and envoplakin is a prominent feature of mature microridges. This interaction is important to integrate actin and intermediate filaments and determines microridge length.

Lamellipodia are another type of cellular protrusion that are formed at the leading edge of migrating cells. In this instance, the cytoskeleton needs to adapt using the guidance cues provided by newly-formed focal adhesion-based attachment sites to the extracellular matrix. Responses of the intermediate filament system have been the subject of many studies revealing modulatory functions depending on intermediate filament isotype and cell type [28]. Vimentin expression is a hallmark feature of migratory cells. The tight crosstalk of vimentin and focal adhesions and the high degree of malleability of vimentin expressing cells may contribute to it [29,30]. It was recently shown, that migration speed and directionality were reduced by treatment of cells with the small chemical compound R491 which interferes with vimentin dynamics [31]. Nestin knock-down in smooth muscle cells also resulted in a reduced migration capacity and focal adhesion size due to reduced Plk1 activation and subsequent vimentin phosphorylation [32]. Overall, intermediate filaments may have a stabilizing function because of their lower turnover in comparison to the other cytoskeletal filament systems enhancing persistence of cell migration [33–36].

Intermediate filaments contribute to the peripheral localization and function of the endoplasmic reticulum

Besides structuring cell shape and surface specializations, intermediate filaments influence the localization and function of organelles by cytoplasmic compartmentalization [37]. Recently, high resolution microscopy revealed that the endoplasmic reticulum is associated with desmosome-anchored keratin filaments [38]. The tubules of the endoplasmic reticulum were oriented along keratin filaments towards desmosomes. Disruption of the keratin network also disrupted the morphology and dynamics of the endoplasmic reticulum and induced the expression of endoplasmic reticulum stress-related markers.

A function of intermediate filaments for the sarcoplasmic reticulum, which is important for cellular calcium handling in skeletal muscle cells, was recently reported [39]. It was shown that the muscle cell-specific intermediate filament polypeptide desmin interacts with the stromal interaction molecule 1 (STIM1), which is a sarcoplasmic reticulum transmembrane protein that controls Ca^{2+} homeostasis. The interaction occurred specifically in regions, where the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) pumps and plasma membrane Orai1 store-operated calcium channels reside. SERCA and Orai1 are known to coordinate Ca^{2+} uptake into the sarcoplasmic reticulum. Since Ca^{2+} handling is also linked to contact sites between mitochondria and the endoplasmic reticulum, it is interesting to note, that loss of the intermediate filament polypeptide nestin in senescent Leydig stem cells leads to a reduction of these contacts [40]. Similarly, mutations in keratin 6 led to reduced mitochondria-endoplasmic reticulum contact sites in keratinocytes [41].

Intermediate filaments protect the nucleus

A cytoplasmic intermediate filament-based “nuclear cage” has been described in multiple cell types. It is a stable ensheathment of the nucleus which appears to be unique in terms of stability and filament organization. It is attached to the lamin-containing nuclear lamina. The attachment is mediated by the cytolinker plectin and the linker of nucleoskeleton and cytoskeleton (LINC) complex, which traverses the nuclear envelope [42–45]. On the cytoplasmic side, the nuclear cage of epithelial cells is connected to the radial spokes which insert into desmosomes and hemidesmosomes serving as a mechanotransductive system [16,46].

Disturbance of the nuclear cage leads to a fragile nucleus in mechanical stress situations. For example, vimentin knock-out fibroblasts are more prone to nuclear envelope rupture and DNA damage during confined migration [47]. In epithelial cells with down-regulated keratin 8 expression, nuclear integrity is compromised as well [45]. Depleting desmin or disrupting the connection of desmin to the nucleus in cardiomyocytes results in massive nuclear infoldings. The effect is linked to dynamic microtubules which surround the nucleus. The nuclear deformations cause changes in gene transcription at the nuclear lamina and induce DNA damage. The authors concluded that desmin is important for mechanical and metabolical homeostasis. The desmin dependent mechanical coupling of the nucleus to the contractile machinery is needed to withstand the ongoing strain imposed by the continuous cycle of contraction and relaxation [43].

Intermediate filament network dynamics are needed for cellular homeostasis

A current research challenge is to understand the different intermediate filament assemblies not only in different cells but even in the same cell signifying specialized intermediate filament properties and functions. A recent paper on the differential antibody accessibility of vimentin's tail domain illustrates this aspect [48]. The authors found that a panel of antibodies recognizing different parts of the tail were able to differentiate between an extended conformation of vimentin that was preferentially detected in loose filaments in the cell periphery and a packed conformation of vimentin that was preferentially detected in more compact filaments in the cell center. The future will show, how this is regulated and how this affects local functionalities in the context of cellular homeostasis.

The cytoplasmic intermediate filament network furthermore unites two apparently contradicting properties: It confers stability supporting the maintenance of cell type- und function-dependent shape while also retaining the ability for remodeling during development, differentiation and stress response. This is achieved by constant network turnover, which can be reversibly regulated at high spatial and temporal precision [49]. The turnover is coupled to multiple mechanisms involving not only local subunit exchange (see above) but also biosynthesis, degradation, and transport. An instructive example of the combined action of degradation and transport was reported for the E3 ligase adaptor protein gigaxonin, which targets intermediate filament polypeptides for proteasomal degradation [50]. Mutations in gigaxonin have been identified in giant axonal neuropathy, which is characterized by large intermediate filament-containing aggregates in neurons that lead to extreme axonal swelling and subsequent cell death. While the phenotype was initially solely linked to reduced intermediate filament degradation, it was recently further shown to be linked to perturbed kinesin-1 dependent transport of intermediate filaments along microtubules. The authors propose that in the absence of gigaxonin, the increase in soluble intermediate filaments sequesters a yet unknown kinesin-1 adaptor and thereby prevents transport and proper distribution of insoluble intermediate filaments, which subsequently form the pathognomonic aggregates.

Intermediate filaments determine axonal conduction velocity

A unique structure-function relationship has been worked out in neurons. Neuronal intermediate filament polypeptides are synthesized in the perikaryon and are subsequently transported into the axon. The polypeptide composition and amounts of neuronal intermediate filaments determine axonal diameter which directly correlates with axonal conduction velocity. Knock-out experiments in mice confirmed this notion [51].

Elongated neurofilament particles have been detected in axons of cultured neurons. They were shown to move bidirectionally along microtubules with an anterograde bias and intermittent stops [52]. The bidirectional transport appears to be important for the longitudinal alignment and straightening of neurofilaments to allow unobstructed transport of other microtubule-motor protein cargoes [53]. With the help of transgenic mice expressing neurofilament protein M fused to a photoactivatable fluorophore, the direction and speed of neurofilament transport could be measured in vivo in myelinated axons of the tibial nerve [53,54]. It was further observed that the majority of the neurofilament pool is mobile [55]. The frequency of active neurofilament transport was dependent on phosphorylation [56]. Furthermore, it was observed that neurofilament transport accelerates locally at nodes of Ranvier [54]. The local constriction is coupled to reduced neurofilaments and increased approximation to microtubules which increases the probability of neurofilament particles to latch onto microtubules.

Conclusions

Taken together, we conclude that the divergent architectural configurations and dynamic properties of intermediate filament networks support specialized functions depending on the cell type and the subcellular localization. The architectural changes are brought about by posttranslational modifications, interactions with intermediate filament-associated proteins and changes in intermediate filament polypeptide expression which occur at different time and length scales. This allows environmental conditioning of the intermediate filament cytoskeleton with its multifaceted modulatory roles.

Author contribution

All authors contributed to the conceptualization and writing of the manuscript.

Funding

The work was funded by the Deutsche Forschungsgemeinschaft (LE556/18-1; LE566/22-2/SPP1782; 363055819/GRK2415).

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.

Acknowledgements

We thank Adam Breitscheidel for expert figure preparation.

References

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

* of special interest
** of outstanding interest

1. Etienne-Manneville S: **Cytoplasmic intermediate filaments in cell biology**. *Annu Rev Cell Dev Biol* 2018, **34**:1–28.

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

3. Yoon M, Moir RD, Prahlad V, Goldman RD: **Motile properties of vimentin intermediate filament networks in living cells**. *J Cell Biol* 1998, **143**:147–157.

4. Chan WK-H, Yabe JT, Pimenta AF, Ortiz D, Shea TB: **Growth cones contain a dynamic population of neurofilament subunits**. *Cell Motil Cytoskeleton* 2003, **54**:195–207.

5. Helfand BT, Chang L, Goldman RD: **Intermediate filaments are dynamic and motile elements of cellular architecture**. *J Cell Sci* 2004, **117**:133–141.

6. Windoffer R, Kölsch A, Wöll S, Leube RE: **Focal adhesions are hotspots for keratin filament precursor formation**. *J Cell Biol* 2006, **173**:341–348.

7. Kölsch A, Windoffer R, Würflinger T, Aach T, Leube RE: **The keratin-filament cycle of assembly and disassembly**. *J Cell Sci* 2010, **123**:2266–2272.

8. Windoffer R, Wöll S, Strnad P, Leube RE: **Identification of novel principles of keratin filament network turnover in living cells**. *Mol Biol Cell* 2004, **15**:2436–2448.

9. Gregor M, Osmanagic-Myers S, Burgstaller G, Wolfram M, Fischer I, Walko G, Resch GP, Jörgl A, Herrmann H, Wiche G: **Mechanosensing through focal adhesion-anchored intermediate filaments**. *FASEB J* 2014, **28**:715–729.

10. Leube RE, Moch M, Windoffer R: **Intermediate filaments and the regulation of focal adhesion**. *Curr Opin Cell Biol* 2015, **32**: 13–20.

11. Moch M, Schwarz N, Windoffer R, Leube RE: **The keratin–desmosome scaffold: pivotal role of desmosomes for keratin network morphogenesis**. *Cell Mol Life Sci* 2020, **77**: 543–558.

12. Moch M, Leube RE: **Hemidesmosome-related keratin filament bundling and nucleation**. *Int J Mol Sci* 2021, **22**:2130.

13. Kim Y-B, Hlavaty D, Maycock J, Lechler T: **Roles for Ndel1 in keratin organization and desmosome function**. *Mol Biol Cell* 2021, **32**. ar2.

14. Colakoğlu G, Brown A: **Intermediate filaments exchange subunits along their length and elongate by end-to-end annealing**. *J Cell Biol* 2009, **185**:769–777.

15. Latorre E, Kale S, Casares L, Gómez-González M, Uroz M, Valon L, Nair RV, Garreta E, Montserrat N, Del Campo A, *et al.*: **Active superelasticity in three-dimensional epithelia of controlled shape**. *Nature* 2018, **563**:203–208.

16. 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.

17. * Prechova M, Adamova Z, Schweizer A-L, 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**, e202105146.

This study demonstrates that the cytolinker plectin contributes to the arrangement of keratin filaments into a circumferential rim and radial spokes and their linkage to desmosomes. The absence of plectin results in tensional disequilibrium and leads to reduced epithelial sheet cohesion.

18. * Wu H, Shen Y, Sivagurunathan S, Weber MS, Adam SA, Shin JH, Fredberg JJ, Medalia O, Goldman R, Weitz DA: **Vimentin intermediate filaments and filamentous actin form unexpected interpenetrating networks that redefine the cell cortex**. *Proc Natl Acad Sci U S A* 2022, **119**, e2115217119.

This work beautifully shows a surprising intertwining of filamentous actin and vimentin intermediate filaments.

19. González-Jiménez P, Duarte S, Martínez AE, Navarro-Carrasco E, Lalioti V, Pajares MA, Pérez-Sala D: **Vimentin single cysteine residue acts as a tunable sensor for network organization and as a key for actin remodeling in response to oxidants and electrophiles**. *Redox Biol* 2023, **64**:102756.

20. Wang Y, Liao G, Wu Y, Wang R, Tang DD: **The intermediate filament protein nestin serves as a molecular hub for smooth muscle cytoskeletal signaling**. *Respir Res* 2023, **24**:157.

21. Jiu Y, Peränen J, Schaible N, Cheng F, Eriksson JE, Krishnan R, Lappalainen P: **Vimentin intermediate filaments control actin stress fiber assembly through GEF-H1 and RhoA**. *J Cell Sci* 2017, **130**:892–902.

22. Ge R, Cao M, Chen M, Liu M, Xie S: **Cytoskeletal networks in primary cilia: current knowledge and perspectives**. *J Cell Physiol* 2022, **237**:3975–3983.

23. Morales EA, Gaeta I, Tyska MJ: **Building the brush border, one microvillus at a time**. *Curr Opin Cell Biol* 2023, **80**:102153.

24. Geisler F, Coch RA, Richardson C, Goldberg M, Bevilacqua C, Prevedel R, Leube RE: **Intestinal intermediate filament polypeptides in C. elegans: common and isotype-specific contributions to intestinal ultrastructure and function**. *Sci Rep* 2020, **10**:3142.

25. Pinto CS, Khandekar A, Bhavna R, Kiesel P, Pigino G, Sonawane M: **Microridges are apical epithelial projections formed of F-actin networks that organize the glycan layer**. *Sci Rep* 2019, **9**:12191.

26. Inaba Y, Chauhan V, van Loon AP, Choudhury LS, Sagasti A: **Keratins and the plakin family cytolinker proteins control the length of epithelial microridge protrusions**. *eLife* 2020, **9**, e58149.

27. Lu TQ, van Loon AP, Sagasti A: **How to wrinkle a cell: emerging mechanisms of microridge morphogenesis**. *Curr Opin Cell Biol* 2022, **76**:102088.

28. Leduc C, Etienne-Manneville S: **Intermediate filaments in cell migration and invasion: the unusual suspects**. *Curr Opin Cell Biol* 2015, **32**:102–112.

29. Guo M, Ehrlicher AJ, Mahammad S, Fabich H, Jensen MH, Moore JR, Fredberg JJ, Goldman RD, Weitz DA: **The role of vimentin intermediate filaments in cortical and cytoplasmic mechanics**. *Biophys J* 2013, **105**:1562–1568.

30. Terriac E, Coceano G, Mavajian Z, Hageman TAG, Christ AF, Testa I, Lautenschläger F, Gad AKB: **Vimentin levels and serine 71 phosphorylation in the control of cell-matrix adhesions, migration speed, and shape of transformed human fibroblasts**. *Cells* 2017, **6**:2.

31. Kim HR, Warrington SJ, López-Guajardo A, Al Hennawi K, Cook SL, Griffith ZDJ, Symmes D, Zhang T, Qu Z, Xu Y, *et al.*: **ALD-R491 regulates vimentin filament stability and solubility, cell contractile force, cell migration speed and directionality**. *Front Cell Dev Biol* 2022:10.

32. Wang R, Khan S, Liao G, Wu Y, Tang DD: **Nestin modulates airway smooth muscle cell migration by affecting spatial rearrangement of vimentin network and focal adhesion assembly**. *Cells* 2022, **11**:3047.

33. De Pascalis C, Pérez-González C, Seetharaman S, Boëda B, Vianay B, Burute M, Leduc C, Borghi N, Trepat X, Etienne-Manneville S: **Intermediate filaments control collective migration by restricting traction forces and sustaining cell–cell contacts**. *J Cell Biol* 2018, **217**:3031–3044.

34. Gan Z, Ding L, Burckhardt CJ, Lowery J, Zaritsky A, Sitterley K, Mota A, Costigliola N, Starker CG, Voytas DF, *et al.*: **Vimentin intermediate filaments template microtubule networks to enhance persistence in cell polarity and directed migration**. *Cell Syst* 2016, **3**:252–263.e8.

35. 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.

36. ** Uceda-Castro R, van Asperen JV, Vennin C, Sluijs JA, van Bodegraven EJ, Margarido AS, Robe PAJ, van Rheenen J, Hol EM: **GFAP splice variants fine-tune glioma cell invasion and tumour dynamics by modulating migration persistence**. *Sci Rep* 2022, **12**:424.
The study uncovers GFAP splice variant-specific regulation of glioma cell invasion in brain slices and in vivo. The findings are in agreement with the correlation of GFAP splice variant ratio and glioma grading.

37. Schwarz N, Leube RE: **Intermediate filaments as organizers of cellular space: how they affect mitochondrial structure and function**. *Cells* 2016, **5**.

38. ** Bharathan NK, Giang W, Hoffman CL, Aaron JS, Khuon S, Chew T-L, Preibisch S, Trautman ET, Heinrich L, Bogovic J, *et al.*: **Architecture and dynamics of a desmosome-endoplasmic reticulum complex**. *Nat Cell Biol* 2023, **25**:823–835.
The beautiful publication employs high-resolution multidimensional light and electron microscopy to uncover the functional interdependency of desmosomes, keratins and the endoplasmic reticulum in a unique spatial arrangement.

39. Zhang H, Bryson VG, Wang C, Li T, Kerr JP, Wilson R, Muoio DM, Bloch RJ, Ward C, Rosenberg PB: **Desmin interacts with STIM1 and coordinates Ca^{2+} signaling in skeletal muscle**. *JCI Insight* 2021, **6**.

40. Yao S, Wei X, Deng W, Wang B, Cai J, Huang Y, Lai X, Qiu Y, Wang Y, Guan Y, *et al.*: **Nestin-dependent mitochondria-ER contacts define stem Leydig cell differentiation to attenuate male reproductive ageing**. *Nat Commun* 2022, **13**:4020.

41. Lehmann SM, Leube RE, Schwarz N: **Keratin 6a mutations lead to impaired mitochondrial quality control**. *Br J Dermatol* 2020, **182**:636–647.

42. Wilhelmsen K, Litjens SHM, Kuikman I, Tshimbalanga N, Janssen H, van den Bout I, Raymond K, Sonnenberg A: **Nesprin-3, a novel outer nuclear membrane protein, associates with the cytoskeletal linker protein plectin**. *J Cell Biol* 2005, **171**:799–810.

43. Heffler J, Shah PP, Robison P, Phyo S, Veliz K, Uchida K, Bogush A, Rhoades J, Jain R, Prosser BL: **A balance between intermediate filaments and microtubules maintains nuclear architecture in the cardiomyocyte**. *Circ Res* 2020, **126**:e10–e26.

44. * Vahabikashi A, Sivagurunathan S, Nicdao FAS, Han YL, Park CY, Kittisopikul M, Wong X, Tran JR, Gundersen GG, Reddy KL, *et al.*: **Nuclear lamin isoforms differentially contribute to LINC complex-dependent nucleocytoskeletal coupling and whole-cell mechanics**. *Proc Natl Acad Sci U S A* 2022, **119**, e2121816119.
The study highlights the relevance of coupling the vimentin cytoskeleton to the nuclear lamina via the LINC complex for cell mechanics and assign different functions in this cross-talk to A- and B-type lamins.

45. * Stenvall C-GA, Nyström JH, Butler-Hallissey C, Jansson T, Heikkilä TRH, Adam SA, Foisner R, Goldman RD, Ridge KM, Toivola DM: **Cytoplasmic keratins couple with and maintain nuclear envelope integrity in colonic epithelial cells**. *Mol Biol Cell* 2022, **33**:ar121.
The authors report on the cross-talk between the nuclear lamina and the keratin cytoskeleton finding a correlation between lamin and keratin 8 expression in colonic enterocytes, which is accompanied by changes in the LINC complex and mechanical resilience of the nucleus.

46. ** 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**, eabd6187.
The authors work out how the keratin cytoskeleton responds to extracellular matrix rigidity and transmits mechanical signals to the nucleus.

47. Patteson AE, Vahabikashi A, Pogoda K, Adam SA, Mandal K, Kittisopikul M, Sivagurunathan S, Goldman A, Goldman RD, Janmey PA: **Vimentin protects cells against nuclear rupture and DNA damage during migration**. *J Cell Biol* 2019, **218**:4079–4092.

48. ** Lois-Bermejo I, González-Jiménez P, Duarte S, Pajares MA, Pérez-Sala D: **Vimentin tail segments are differentially exposed at distinct cellular Locations and in response to stress**. *Front Cell Dev Biol* 2022, **10**:908263.
The authors very carefully dissect the accessibility of segments of vimentin's tail domain in different subcellular regions and during lipoxidative stress. It is proposed that the observed versatility in filament subdomain arrangement enhances the capability to fine-tune intermediate filament dynamics.

49. Di Russo J, Magin TM, Leube RE: **A keratin code defines the textile nature of epithelial tissue architecture**. *Curr Opin Cell Biol* 2023, **85**:102236.

50. * Renganathan B, Zewe JP, Cheng Y, Paumier J-M, Kittisopikul M, Ridge KM, Opal P, Gelfand VI: **Gigaxonin is required for intermediate filament transport**. *FASEB J Off Publ Fed Am Soc Exp Biol* 2023, **37**, e22886.
The study presents evidence for a function of the E3 ligase adaptor gigaxonin in kinesin-1-mediated intermediate filament transport.

51. Yuan A, Rao MV, Veeranna, Nixon RA: **Neurofilaments and neurofilament proteins in health and disease**. *Cold Spring Harbor Perspect Biol* 2017, **9**:a018309.

52. Wang L, Ho C, Sun D, Liem RKH, Brown A: **Rapid movement of axonal neurofilaments interrupted by prolonged pauses**. *Nat Cell Biol* 2000, **2**:137–141.

53. Boyer NP, Julien J-P, Jung P, Brown A: **Neurofilament transport is bidirectional in vivo**. *eNeuro* 2022, **9**.
*
This work together with the work in reference 55 provides in vivo evidence for bidirectional transport of neurofilaments in dissected tibial nerves.

54. Walker CL, Uchida A, Li Y, Trivedi N, Fenn JD, Monsma PC, Lariviére RC, Julien J-P, Jung P, Brown A: **Local acceleration of neurofilament transport at nodes of ranvier**. *J Neurosci* 2019, **39**:663–677.

55. Fenn JD, Li Y, Julien J-P, Jung P, Brown A: **The mobility of neurofilaments in mature myelinated axons of Adult mice**. *eNeuro* 2023, **10**. ENEURO.0029-23.2023.
*
See 53.

56. Uchida A, Peng J, Brown A: **Regulation of neurofilament length and transport by a dynamic cycle of phospho-dependent polymer severing and annealing**. *Mol Biol Cell* 2023, https://doi.org/10.1091/mbc.E23-01-0024.