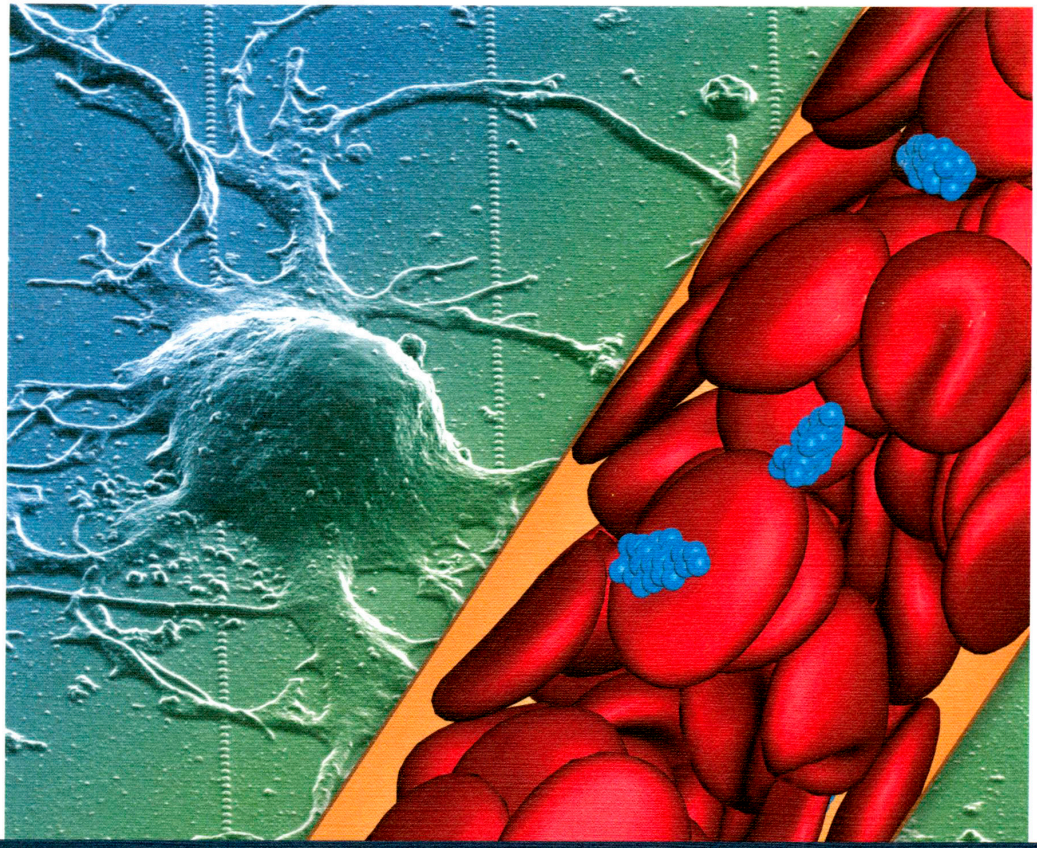

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# D 7 Cell and Tissue Mechanics

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## Contents



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# Introduction

The goal of this lecture is to illustrate, why an understanding of the force balance acting on cells and tissues is important for elucidating mechanisms determing physiology and pathology. The three selected examples highlight different aspects of this theme. Each is of medical relevance and focuses on the contribution of the cytoskeleton and specialized adhesion sites.

First, we will elaborate on cell migration as a cardinal cellular trait that is an intricate feature of developmental processes, immune responses, and tumor cell metastasis. We will concentrate on single cells, that are currently best characterized, and describe an iterative cycle involving the force-generating machinery, which is dynamically linked to the extracellular substrate and involves pulling, pushing and friction. Second, we will describe the keratin-desmosome scaffold of epithelial cells. We will zoom in (*i*) on the subapical network in intestinal cells that is conserved from *C. elegans* to human, and (*ii*) on the 3D network in epidermal cells with its diversified stratum-, context-, and function-dependent molecular composition. We will present evidence, that these systems fullfil important architectural and mechanical functions in their native tissue contexts. Consequently, mutations of the encoded genes result in reduced mechanical resilience leading to pronounced tissue perturbations such as cytoplasmic invaginations and blister formation. Third, we will portray a rare type of cardiomyopathy that has been linked to disruption of cytoskeleton-junction coupling. We will show why it is necessary to understand the mechanical dysfunction for elucidating the still unknown pathomechanism of the disease.

Taken together, we conclude and propose that genetics and chemical microenvironment alone are not sufficient to understand cell and tissue function and that the mechanical microenvironment is just as important in determining cellular function, fate and dysfunction.

# 1 The mechanics of single cell migration

The aim of this part is to describe single cell migration as a paradigm highlighting the effect of forces on single cells. Several of the cellular components and molecular processes have been studied at much detail, since they are accessible to *in vitro* examination in cultured cells.

Migration is a fundamental property of cells. It allows directed movement in response to changes in the microenvironment supporting growth, differentiation and regeneration and, at the same time, avoiding adverse conditions. The cues driving migratory behaviour include chemical signals such as nutrients, growth factors, and toxins or physical signals such as radiation as well as mechanical (gravitational) and electromagnetic forces. Thus, one can distinguish between chemotaxis caused by chemoattractans or morphogens, haptotaxis due to varying substrate concentrations, mechanotaxis because of cell contact breakdown, electrotaxis induced by electric fields and durotaxis caused by differences in substrate stiffness. These cues induce movement of cells in relation to their environment. This requires mechanical forces involving a controllable force-generating machinery that must be linked not only to counterbalances within the cell but also to counterbalances in the outside environment. The force-generating machinery corresponds to the acto-myosin system, whose contractile activity is regulated by inducible signalling pathways. The cytoplasmic counterbalance is provided by the cytoskeleton, which is composed of three major filament systems, each with unique biomechanical, structural, chemical and functional properties

(Table 1). The extracellular counterbalance corresponds to the extracellular matrix. Its biomechanical properties vary considerably through different admixtures of its three major components, i.e. the filamentous component consisting of collagen and elastic fibres, the organic non-filamentous component containing gel-forming glycosaminoglycans, and the anorganic component including calciumphosphate, which contributes to extracellular matrix stiffness. The intra- and extracellular counterbalances are coupled through specific cell-extracellular contacts (Table 2). In addition, the cytoplasmic counterbalances are coupled across cell borders through specialized cell-cell contacts (Table 2).

**Table 1**

| Major cytoplasmic filament systems in human | | | |
|---|---|---|---|
| | **Microtubules** | **Intermediate Filaments** | **Actin Filaments** |
| Diameter | 24 nm | ~10 nm | 7 nm |
| Molecular components | 9 α-tubulins<br>10 β-tubulins | > 70 intermediate filament poly-peptides<br>[epithelia: 28 type I keratins (K9-40) and 26 type II keratins (K1-8, K71-86)] | 6 actins<br>[cytoplasmic: ACTB (cell cortex), ACTG1 (stress fibres); muscle-specific: ACTA1 (skeletal muscle), ACTC1 (cardiac muscle), ACTA2 / ACTG2 (smooth muscle)] |
| Enzymatic activity | GTPase | None | ATPase |
| Building principles | Heterodimers -> 13 proto-filaments<br>-> polarized ((+) and (-) end) | Keratins: heterodimer -> tetramer -> unit length filament -> 10 nm filament<br>-> non-polar | Double helix with 14 subunits per turn<br>-> polarized ((+) and (-) end) |
| De novo formation | Nucleation (microtubule organizing center) -> elongation | Nucleation (spontaneous?) -> elongation (unit length filament addition?) -> network integration (?) | Nucleation -> elongation |
| Assembly / Disassembly | Dynamic instability | Lateral subunit exchange - excision / insertion / annealing - turnover cycle | Treadmilling / retrograde flow - branching (Arp2/3) - plus-end growth (formins) |
| Mechanics | Persistence length: ~1 mm<br>Young's modulus: 1 000-1 500 MPa<br>-> bear high compressive forces<br>-> generate pushing and pulling forces | Persistence length: ~ 1 µm<br>Young's modulus: 6-300 MPa<br>-> elastic deformation at low mechanical load<br>-> plastic deformation at high mechanical load | Persistence length: ~10 µm<br>Young's modulus: 1 800-2 500 MPa<br>-> semiflexible<br>+ myosin: biological active springs |
| Filament localization | - Radial (centrosomal)<br>- Non-centrosomal | - Pancytoplasmic<br>- Perinuclear<br>- Subplasmalemmal | - Filopodial<br>- Lamellipodial/lamellar<br>- Dorsal arcs<br>- Ventral / dorsal stress fibres<br>- Dense bodies (smooth muscle)<br>- Sarcomeric (striated muscle) |
| Filament organization | Single filaments - filament bundles - 3D network | | |
| Superstructures | - Cilium, flagellum<br>- Centrosome/basal body | - Keratohyalin granule<br>- Cornified envelope | - Microvillus<br>- Lamellipodium / filopodium |
| Functions of identified associated proteins | Nucleating<br>Polymerization-inhibiting<br>Solubilizing / destabilizing<br>Stabilizing / co-filamentous<br>Gel-forming / cross-linking<br>Bundling<br>Severing<br>(+) end capping / (-) end capping<br>ATPase (motor protein) | Polymerization-inhibiting<br>Gel-forming / cross-linking<br>Membrane-attaching | Nucleating<br>Polymerization-inhibiting<br>Solubilizing / destabilizing<br>Stabilizing / co-filamentous<br>Gel-forming / cross-linking<br>Bundling<br>Severing<br>(+) end capping / (-) end capping<br>Membrane-attaching<br>ATPase (motor protein) |
| Motor proteins | Kinesins, dyneins | None | Myosins |
| Posttranslational modifications | Phosphorylation, acetylation, sumoylation, ubiquitination, oxidation, glycosylation, methylation, ADP ribosylation | | |
| | Arginylation, detyrosination, polyglycylation, poly-glutamylation, palmitoylation | Transamidation | Arginylation, nitrosylation |
| Depolymerizing / stabilizing drugs | Colchicine, nocodazole, vinblastin, demecolcine / taxol | None | Cytochalasins, latrunculin / jasplakinolide, phalloidin |

**Table 2**

| Composition of major load-bearing junctions in epithelia | | | |
|---|---|---|---|
| | **Major transmembrane proteins** | **Major linker proteins** | **Associated cytoskeletal filaments** |
| Desmosome (Macula adhaerens) | Desmosomal cadherins (desmogleins and desmocollins) | Plakoglobin, plakophilins and desmoplakins | Keratin intermediate filaments |
| Adherens junction | "Classical" cadherins, nectins | Catenins (p120, β, α), vinculin, afadin | Actin filaments |
| | | | |
| Hemidesmosome | Integrins (α6/β4), BP180 | BP230, plectin | Keratin intermediate filaments |
| Focal adhesion | Integrins (multiple α/β isoforms) | Talin, vinculin, kindlin | Actin filaments |

Crawling is the predominant form of cell translocation in animals. Different types of crawling can be distinguished including amoeboid (fast, weak adhesion, poorly developed cytoskeleton) and mesenchymal/epithelial movement (slow, strong adhesion, highly developed cytoskeleton) of single cells and collective migration of cell groups arranged as chains or sheets [1, 2]. Polarization initiates cell migration defining front and rear of cells through partitioning of regulatory molecules leading to the formation of a tail at the back (uropod) and a leading edge in the front (lamellipod). The subsequent canonical mode of mesenchymal/epithelial single cell migration on a flat 2D surface consists of repetitive cycles encompassing (*i*) protrusion, (*ii*) adhesion, (*iii*) cell body translocation, and (*iv*) retraction [3-5]; Fig. 1). Each step involves changes in the local force equilibrium.

(i) **Protrusion** is defined as leading edge extension and starts with filopodial exploration. Filopodia are thin finger-like protrusions (diameter: ~50 nm; length: several μm) of the plasma membrane at the leading edge each containing 15-30 bundled actin filaments [6, 7]. Polymerization/depolymerization of actin filaments at the tip of filopodia determine extension/retraction of these structures which is coordinated by formins. The spike-like filopodia are typically associated with the lamellipodium, the outermost part of the very flat sheet-like part of the cell's leading edge, which is referred to as the lamellum. It is characterized by membrane ruffling that is driven by a branched actin network. The ARP2/3 complex facilitates formation of network branches and fixes them at a 70° angle [8]. Net filament assembly at the leading edge and net filament disassembly behind the leading edge together support protrusion of the leading edge while individual actin filaments remain stationary with respect to the substratum. Forces are generated through attachment of actin stress fibres to focal adhesions by a clutch in a ratchet mechanism [9]. Focal adhesions, in turn are coupled to the extracellular matrix (step ii).

(ii) **Adhesion** is primarily mediated through focal adhesions, which link the actin cytoskeleton to the extracellular matrix. New focal adhesion sites are constantly generated at the leading edge. They go through a process of maturation that is reflected by compositional and structural alterations. Nascent focal adhesions are formed in the transition zone between the lamellipodium and the lamellum forming small focal complexes that become larger and elongated focal adhesions under the influence of forces imposed by associated actin stress fibres and extracellular matrix components [10]. The mechanical coupling, which is subject to regulation, is referred to as the mechancial clutch [9]. Focal adhesions subsequently mature into fibrillar adhesions [11].

(iii) **Cell body translocation** is facilitated by contraction at the rear end through activation of the actomyosin system involving myosin II activity, which propels the cell body forward [3-5].

(iv) **Retraction** is coupled to rear end release via de-adhesion [3-5]. The necessary disassembly of extracellular matrix contacts, however, is not complete. As a consequence long retraction fibres are formed, which are eventually ripped off leaving behind tracks of remnant membrane fragments, which remain attached to the extracellular matrix and contain integrin adhesion molecules.

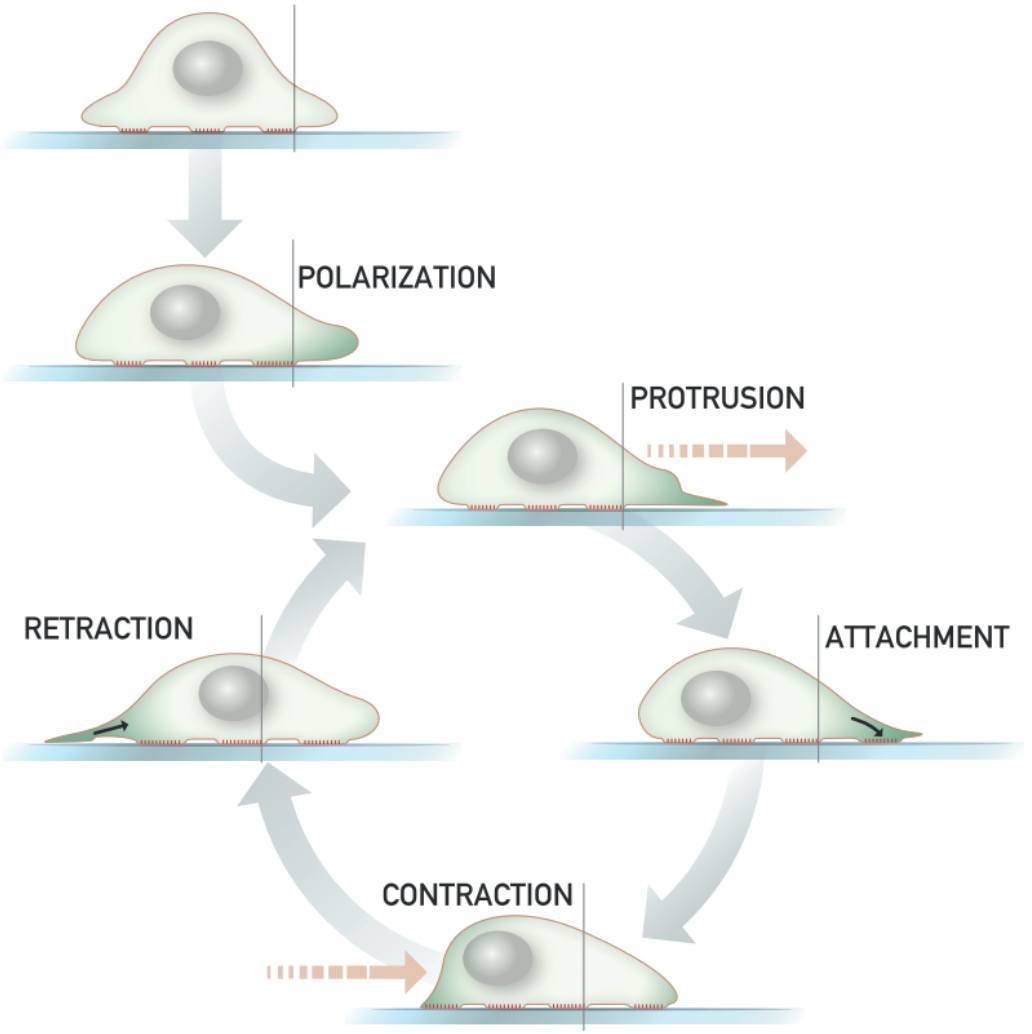


**Fig. 1:** *Schematic representation of the major steps in single cell migration on a flat 2D surface.*

The above processes are coupled to and coordinated by **mechanosensing** and **mechanotransduction** [12-14]. Mechanosensors can transform mechanical signals into biochemical information. The most relevant mechanism for cell migration inolves force-dependent conformational alterations, which open binding domains and enzymatically active domains. The proteins are typically characterized by a modular structure. Forces impose sequential unfolding of tertiary structures within each module. Mechanosensors are integral

parts of the cytoskeleton-extracellular matrix scaffold. Thus, forces facilitate, e.g.: integrin binding of the extracellular matrix protein fibronectin, focal complex maturation by activation of the focal adhesion protein talin, induction of signaling cascades by the focal adhesion protein p130Cas, actin stress fibre formation by the focal adhesion protein zyxin, and cortical actin stabilization through filamin.

Our current knowledge in cell migration is, for the most part, restricted to the actin cytoskeleton and its associated focal adhesions. The precise role of the other cytoskeletal systems is much less understood. Microtubules serve an important function in polarized transport processes needed for membrane and cytoplasmic extension [15]. Intermediate filaments, on the other hand, have been shown to affect cell migration in different ways depending on molecular composition and context [16-18]. Similarly, the role of hemidesmosomes, which anchor intermediate filaments to the extracellular matrix (Table 2), and their interplay with focal adhesions still remains to be elucidated [19].

Cell migration is important for many physiologically occurring processes and pathologies. During embryogenesis, organogenesis and regeneration undifferentiated precursor cells are directed to distant locations. During wound healing and immune responses environmental signals inform cells to move. Migration of the wrong cell type to the wrong place is encountered in pathology with catastrophic effects on tissue homeostasis occurring in autoimmune diseases and during metastasis in carcinogenesis.

# 2 Epithelia: ramparts against mechanical stress

The aim of this part is to describe the keratin intermediate filament-desmosome system as a tissue- and cell-type specific scaffold providing epithelial resilience and supporting epithelial barrier function. Epithelia are exposed interfaces between the outside environment and the body and are therefore subjected to mechanical stress. At the same time, epithelia serve as large surfaces for the bidirectional exchange of molecules between the external and internal milieu by resorption and secretion. Depending on the specific mechanical and functional requirements epithelia encompass not only different cell types but are also distinguished by different tissue architectures ranging from polarized single cell layers to multilayered assemblies (Figs. 2, 3).

Keratin intermediate filaments are major components of the epithelial cytoskeleton. They are attached to desmosomal cell-cell adhesion sites and hemidesmosomal cell-extracellular matrix adhesions. Together they fullfil specific biomechanical tasks within the different epithelia. This is reflected by cell- and epithelial tissue type-specific patterns of keratin and desmosomal protein isoform expression and arrangements [20, 21]. By paradigmatically describing the situation in the single-layered intestinal epithelium and the multilayered epidermal epithelium we will highlight some of the features of the keratin-desmosome scaffold in functional tissue contexts.

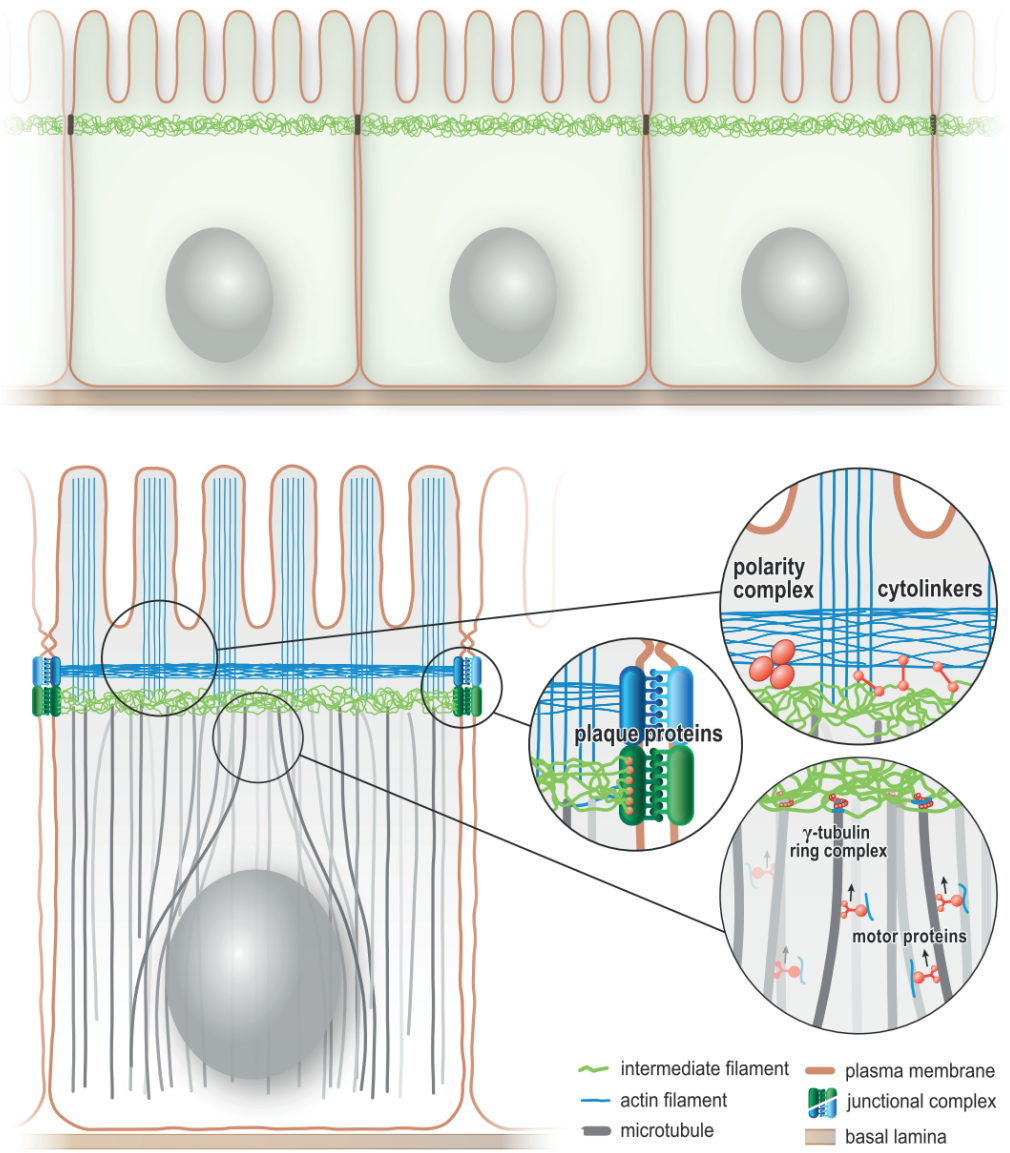


**Fig. 2:** *Scheme depicting organizational aspects of the cytoskeleton and cell adhesions in the one-layered polarized intestinal epithelium. The top part emphasizes the subapical enrichment of ntermediate filaments that are anchored to cell-cell junctions. The bottom part presents features of all three major cytoskeletal filament systems (intermediate filaments, actin filaments, microtubules) that are anchored to junctions through plaque proteins, crosslinked to each other by cytolinkers, enriched at the apical domain together with the polarity complex, delivered to specific regions by motor proteins, and co-distributed through nucleation sites (γ-tubulin ring complex). Further details in [22].*

## 2.1 Single-layered polarized intestinal epithelium

Intestinal epithelia are prototypic single-layered polarized epithelia, which face the body interior at their basal surface and the body exterior at their apical suface. The function of the intestinal epithelium is to facilitate regulated exchange of molecules between the outside, i.e. the intestinal lumen, and the inside of the body while maintaining an intact and resilient barrier between both compartments. Intestinal cells produce a distinct subset of keratin polypeptides including the type II keratins K7 and K8 and the type I keratins K18, K19 and K20 (cf. [22]). K8 and K19 are synthesized throughout the epithelium of the small and large intestine. But the other keratins show a more restricted distribution with K18 and small amounts of K7 primarily in the undifferentiated crypt compartment and K20 in the villus. Differential distribution of desmosomal proteins along the crypt-villus axis has also been reported for desmosomal proteins [23]. It will be interesting to find out how the differing molecular composition relates to differences in local cellular specialization and properties, whereby cells differentiate and move from the crypt to the villar tip where they are constantly shed into the intestinal lumen.

A remarkable architectural feature of the intestinal keratin cytoskeleton is its concentration below the adluminal plasma membrane separating the apical organelle-free terminal web region containing the microvillar rootlets of bundled actin filaments from the rest of the cytoplasm (Fig. 2). This arrangement is conserved from human all the way to the nematode *C. elegans*, in which six intestine-specific intermediate filament polypeptides form a very dense subapical network that is anchored to the *C. elegans* apical junction, a multicomponent cell-cell adhesion complex [22, 24]. Local perturbations of the network or collapse of the network towards the junction leads to luminal widening and cytoplasmic invaginations of the apical plasma membrane [25, 26]. These phenotypes tend to aggravate with increasing age. The most likely explanation is reduced mechanical stability of the intermediate filament-rich structure, which succumbs to chronic wear and tear. This hypothesis has been tested on vital intestine. The intestine can be easily prepared from living worms by a single cut, which results in its extrusion. Using a dual micropipette assay the dissected intestine is then accessible for stress-strain analyses. This revealed a remarkable resilience of the intestine along the longitudinal axis preventing ruptures at applied forces of up to 0.37 μN [27]. It further showed that increased strain is observed at high forces of mutant intestines (own unpublished results).

## 2.2 Multilayered epidermal epithelium

The epidermis consists of multiple layers with stratum-specific differentiation features (Fig. 3). The basal layer consists of cylindrical cells that are attached to the basement membrane through hemidesmosomes. The cells divide to maintain and replenish not only the basal but also all suprabasal compartments. The first suprabasal compartment is referred to as the spinous layer. It is no longer in contact with the basement membrane and is characterized by increasingly flat cells that are circumferentially surrounded by abundant desmosomes. The next layer is the stratum granulosum, which contains prominent cytoplasmic granules. The top layers are formed upon programmed cell death (apoptosis) coupled to the formation of the cross-linked envelope, which serves as a protective barrier. The various differentiation states are reflected by different keratin expression profiles [21]. Keratins K5 and K14 are obligatory components of basal keratinocytes. In addition, K15 is often detectable with predilection for stem cells, most notably in the hair follicle bulge. On the other hand, K1 and K10 are usually found in suprabasal cells. They are complemented by K2 and K24 in the upper spinous and

granular layer [28] and by keratin 78 in the basal and first suprabasal layer [29]. Of note K9 is only produced in the mechanically most challenged palmoplantar epidermis. Other keratins such as K6, K16 and K17 are absent in the normal interfollicular epidermis of hairy skin but are switched on in certain situations, notably upon wounding, which requires movement of keratinocytes towards the lesioned area and keratinocyte proliferation. It is generally assumed that the different keratins endow cells with specific biomechanical properties. Thus, the different keratin pairs exhibit different biochemical properties (polymer stability, end domain composition) and differ in their propensity to bundle and to associate with desmosomes (e.g., [30, 31]).

Desmosomes are highly abundant in the epidermis occupying the major part of the surface of suprabasal cells and increasing in size towards the uppermost layers, where they form large corneodesmosomes. Compositionally, desmosomes also differ in the various epidermal layers thereby further fine-tuning the properties of the epidermal keratin-desmosome system [20, 32]. Taken together, the cytoplasmic keratin network in conjunction with its desmosomal anchorage sites form a transcellular network that is believed to confer epidermal resilience and plasticity. We recently proposed that this system is based on an ordered arrangement of the keratin network consisting of perinuclear filaments that are linked through radial spokes to desmosomes, which are, in turn, connected to each other by suplasmalemmal keratin filaments (the rim; [33]).

The most convincing evidence for a mechanical function of the keratin-desmosome scaffold stems from human blistering diseases that have been linked to desmosomal proteins and intermediate filament proteins [20, 31, 34, 35]. As an example, we will describe features of *epidermolysis bullosa simplex*, which is an autosomal dominant disease that has been linked to single point mutations in the genes encoding K5 and K14 [31, 36-38]. Patients develop blisters in mechanically challenged regions. The blisters are restricted to the basal cell layer, where cytolysis occurs. This is linked to the formation of prominent keratin aggregates. The most common assumption is that the keratin point mutations encode keratin polypeptides acting in a dominant-negative fashion on keratin filament network assembly. In accordance, transfection of these mutant keratin has been shown by many laboratories to induce abundant granule formation and loss of keratin filaments. It is further assumed that dysfunctional keratin networks lead to the increased sensitivity of basal keratinocytes to mechanical trauma resulting in cytolysis and blister formation. While the simplicity of this argument and the copious evidence are overwhelming and highly seductive, the pathogenesis may be more complicated. Thus, (*i*) some of the most severe mutations do not prevent keratin filament formation *in vitro*, (*ii*) *epidermolysis bullosa simplex* patients develop normal-appearing keratin-desmosome scaffolds in non-traumatized regions, and (*iii*) patients with mutations in suprabasal keratins do not primarily develop blisters but present with hyperkeratosis. As an alternative mechanism, we have recently shown that phophomimetic mutation of a single residue is sufficient to prevent keratin filament network formation [39]. Therefore, altered mechanosensing and mechanotransduction likely contribute to the full penetrance of the *epidermolysis bullosa simplex* phenotype.

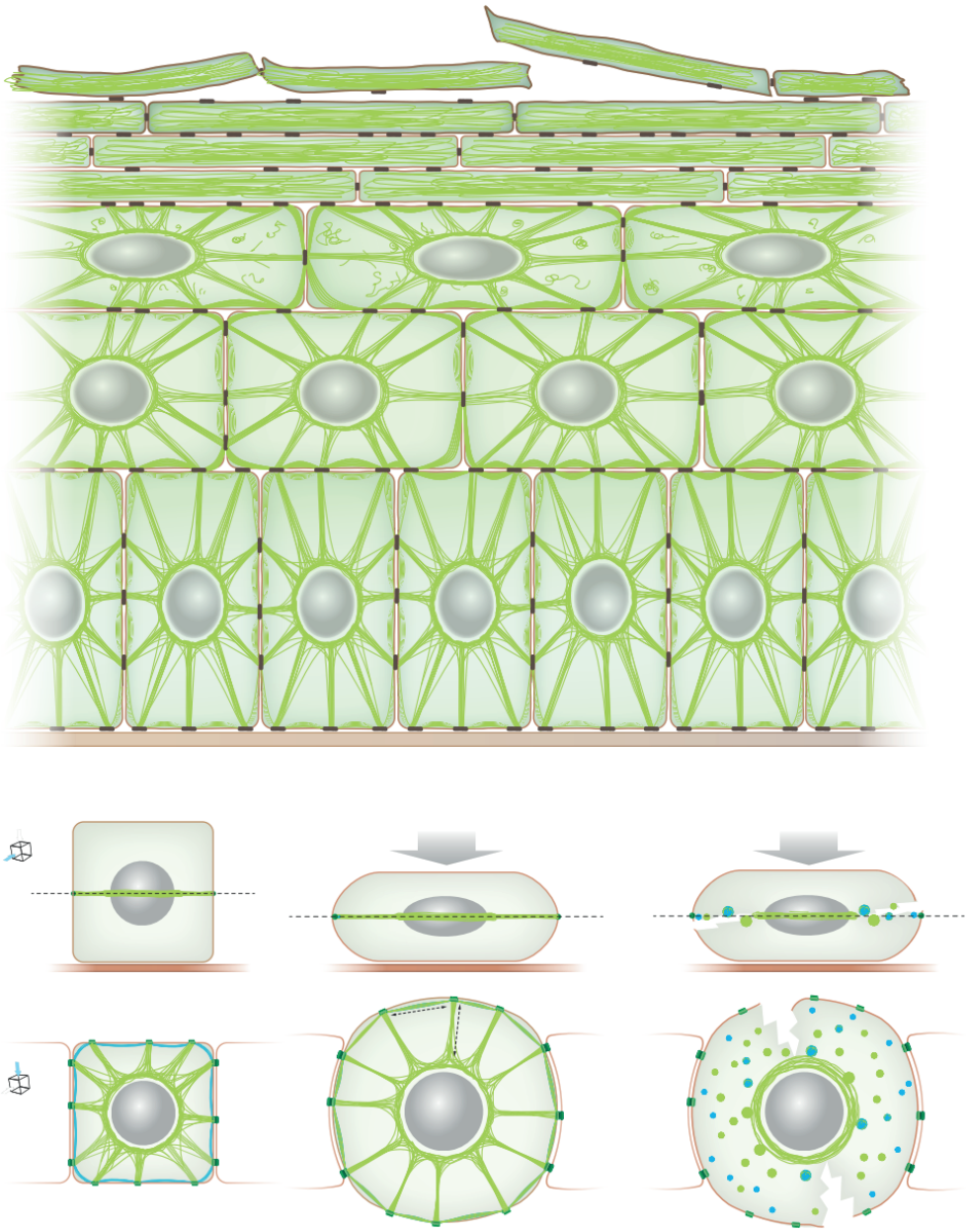

**Fig. 3:** *Scheme depicting organizational aspects of the keratin cytoskeleton and its desmosomal/hemidesmosomal anchorage sites in the multilayered epidermal epithelium at steady state and upon increased pressure under normal circumstances (middle lower panel) or in the presence of keratin mutations causing epidermolysis bullosa simplex (right lower panel). Lack of keratin-mediated desmosomal connectivity results in cytolysis and subsequent blister formation [further details in [33]].*

# 3 Heart muscle: The challenges of permanent contraction cycles

As a last example, we highlight the importance of cell adhesion and the cytoskeleton in the heart. The heart is unique by performing incessant cycles of contraction and relaxation throughout life at regular intervals. Thus, an 80 year-old heart beating at an average rate of 60 times per minute has gone through ~$2.5x10^9$ precisely timed and coordinated contraction/relaxation cycles. This is made possible by a highly ordered arrangement of the contractile apparatus that is functionally and mechanically coupled between adjacent cardiomyocytes (Fig. 4). Specialized cell-cell contacts, i.e. the intercalated discs, are masterpieces of efficiency to realize the necessary electromechanical coupling. The intercalated disc connects neighbouring contractile and excitable cardiomyocytes by a complex arrangement of different cell-cell junctions, which are tightly interwoven within this superstructure. Stripe-like *fasciae adhaerentes* serve as anchorage sites for the contractile acto-myosin apparatus. Dot-like desmosomes facilitate attachment of desmin intermediate filaments, which enwrap the contractile system. Gap junctions (*nexus*) form transcellular channels and mediate electrical coupling.

Arrhythmogenic cardiomyopathy (AC) is a rare cardiomyopathy that has been linked to mutations of all known desmosomal proteins that are synthesized in the heart [40, 41]. Arrhythmias are the first symptoms which can lead to sudden death, occurring occasionally during endurance sports. In most cases, however, foci with necrotic cardiomyocytes appear during the acute disease stage that are replaced by fibrofatty tissue. During the chronic disease phase dilative cardiomyopathy is most prominent. The pathology is often restricted to the right ventricle but may also affect the left ventricle. Heart failure may eventually necessitate heart transplantation. Different disease mechanisms have been discussed, none of which has been conclusively affirmed by the scientific community [40, 41].

An idea favored by several researchers is that a dysfunction in adhesion triggers the disease [42-44]. In support, a reduced number of desmosomes and widened intercellular gaps have been observed in tissue samples of AC patients and murine AC models which were interpreted as indications of reduced adhesion strength [42, 43, 45]. Given that desmin mutations also induce an AC phenotype (c.f. [41]), it will be important to examine the biomechanical function of the entire cardiac desmin intermediate filament-desmosome scaffold. It may be a safeguarding system, which keeps the ordered sarcomeric structure and cellular organelles such as mitochondria in place because of its intrinsic elasticity and recoil activity. Obviously, the desmosomal protein mutations do not interfere directly with cardiac contractility and function, since homozygous mutant mice carrying the disease-causing mutations still develop normal-appearing hearts. As mechanical load increases, however, the disease develops postnatally. Thus, focal cardiomyocyte necrosis is observed during adolescent growth. The necrosis elicits an aseptic inflammatory reaction which eventually leads to scar formation and thereby alters extracellular matrix stiffness. This pathology may be the consequence of acute and localized excessive mechanical stress leading to disruption of cardiomyocyte connectivity. Later on, cardiac dilation is the most prominent feature that is coupled to a reactive hypertrophic response [46]. Major difficulties in unravelling the underlying molecular mechanisms are the lack of appropriate *in vitro* model systems and the relative inaccessibility of the actively moving cardiac muscle *in vivo*. Elucidation of molecular architecture of the cytoskeleton and its associated anchorage sites at cell-cell contacts (intercalated disc) and cell-extracellular matrix contacts (costamere) at high

resolution in 3D, biomechanical probing of cardiac tissue slices, and functional *in vivo* imaging, however, may help to improve our understanding of the altered mechanics in the AC heart.

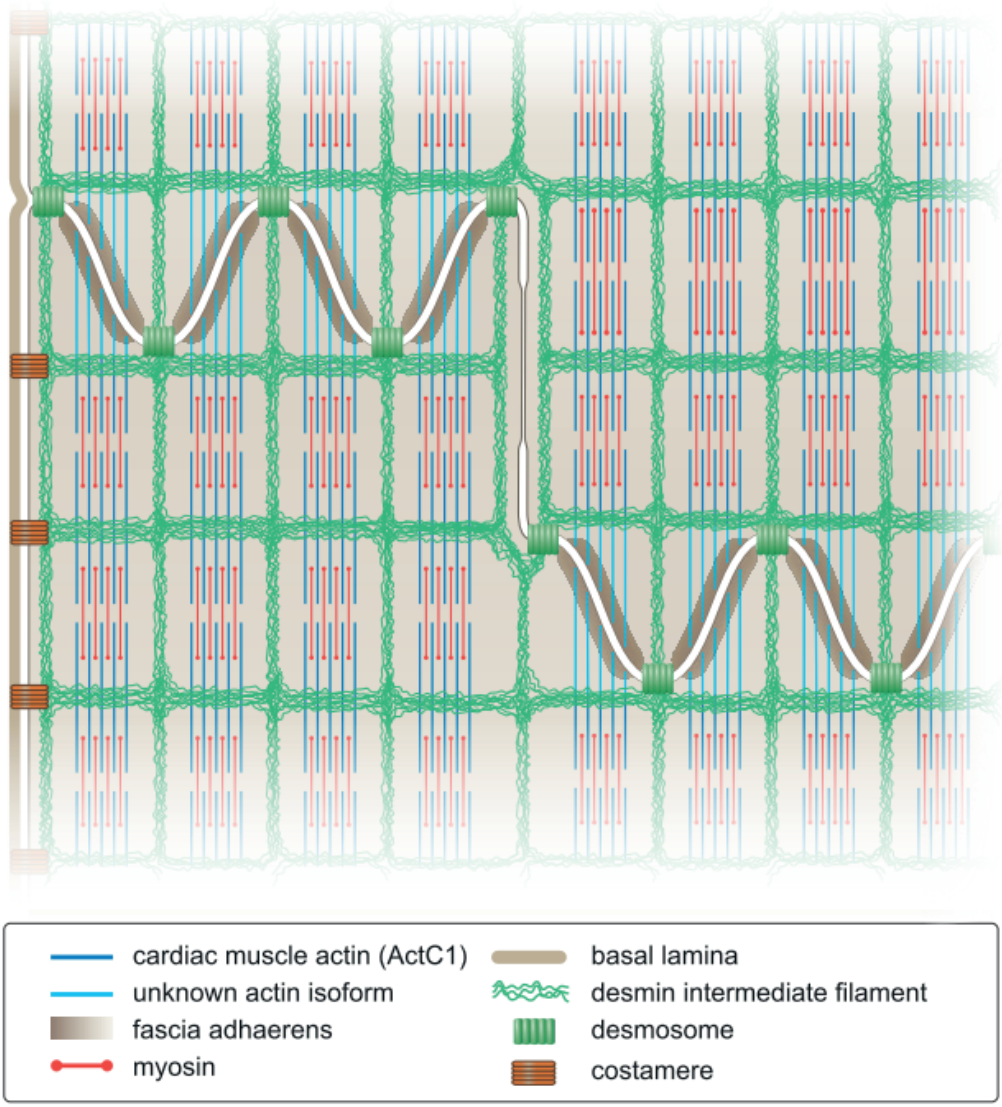


**Fig. 4:** *Scheme of the intercalated disc as an integrator of mechanical forces and signal transducer between adjacent cardiomyocytes.*

# 4 Summary and conclusions

The three examples were selected to highlight the importance of cellular mechanical stability in single cells and, more importantly, in differentiated tissue. We wanted to emphasize that the cytoskeleton and its associated adhesion sites are crucial prerequisites for cellular mobility on the one hand and maintenance of tissue integrity on the other hand. Our knowledge of the

force distribution at the cellular and subcellular level is still rather limited but it is crucial to elucidate the contribution of specific molecules. A fascinating challenge is to understand how forces are sensed and translated into cellular responses. The advent of highly sensitive devices to measure and locally modify the force equilibrium herald exciting discoveries in the growing field of mechanobiology. These discoveries will help to elucidate pathomechanisms in numerous diseases and open novel avenues for the treatment of various pathologies.

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