Topical Review

Physical role for the nucleus in cell migration

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Abstract

Cell migration is important for the function of many eukaryotic cells. Recently the nucleus has been shown to play an important role in cell motility. After giving an overview of cell motility mechanisms we review what is currently known about the mechanical properties of the nucleus and the connections between it and the cytoskeleton. We also discuss connections to the extracellular matrix and mechanotransduction. We identify key physical roles of the nucleus in cell migration.

Keywords: nucleus, cell migration, mechanics

(Some figures may appear in colour only in the online journal)

1. Introduction

Cell migration is of crucial importance in development, the immune system, wound healing and cancer metastasis. It is therefore a topic of great interest not just in biology but also due to its potential applications in medicine and technology. As we will highlight in this article there are many reasons why physical scientists are also increasingly interested in this area of biological physics.

This review focuses on the physical role of the nucleus in eukaryotic cell migration. The role of the nucleus has been largely neglected, partly due to the famous experiments of keratocyte cell fragments crawling without a nucleus [1]. Recently however the nucleus has been shown to play an important role in cell motility, especially in three dimensional environments [2]. The nucleus is connected to the cell cytoskeleton which is known to play a key role in cell migration. Cytoskeleton elements interact with the external environment, for example through specific adhesion. Therefore, the nucleus is in contact with the external environment via the cytoskeleton. These interactions provide the basis for mechanosensitivity and force transduction from the external environment to the nucleus, which plays an important role in cell migration. The nucleus is not only an object that has to be transported with the cell, but it is also connected to the migration machinery. Nuclear positioning within the cell is important in cell polarisation, setting the direction of motion. In addition, the nucleus is more solid-like than the rest of the cell and consequently less deformable. This resistance to deformation can hinder cells squeezing through constrictions. The role of the nucleus in cell migration is of particular interest in metastatic cancer cells, whose nuclei have abnormal shapes and stiffnesses.

In this article we first give an overview of cell motility mechanisms (section 2) and then discuss the mechanical properties of the nucleus (section 3) and the connections between the nucleus, cytoskeleton and extracellular matrix (section 4). In section 5 we discuss the roles of the nucleus in migrating cells, in particular nuclear positioning in cell polarisation, nucleus-cytoskeleton connection dependent migration and nucleus deformation during migration in confinement. Finally in section 6 we provide a summary and outline some key unanswered questions.

2. Overview of cell motility mechanisms

A general overview of cell motility for physical scientists is given by [3]. Here we focus on eukaryotic cells and ignore motility due to flagella. Cell migration was first observed
using microscopes in the 1600s by scientists such as Robert Hooke and Antonie van Leeuwenhoek. Early experiments on cell migration investigated cells crawling on flat glass substrates, since this is ideal for optical microscopy. To enable cell adhesion to the substrate the glass coverslip is coated with extracellular matrix protein (e.g. fibronectin or collagen). In some experiments cells polarise spontaneously in random directions. However, polarisation and migration direction can be directed for example by imposing gradients of chemotactants to which cells respond. Other ways to direct cells have been studied more recently such as adhesion micropatterning [4] or gradients of substrate stiffness (durotaxis) [5]. Many different aspects of such cell crawling assays have been studied in great detail. In this review we focus on the motile stage and we refer readers elsewhere to more detailed reviews on adhesion [6, 7], spreading [8], polarisation [9, 10] and chemotaxis [11].

It is clear that the networks of filamentous proteins making up the cytoskeleton are crucial for the mechanical properties, shape and migration of cells. Microtubules and actin have been studied in most detail, but the contribution of intermediate filaments and septins are increasingly being studied [12]. Of particular importance in cell motility is the protein filament actin and the molecular motor myosin. Visualisation, for example using fluorescence microscopy, of these various proteins within live migrating cells and disruption of different components by genetic or drug treatments have contributed greatly to discovering the roles of these proteins in cell motility.

The classic picture of cell crawling is of a polarised cell with a wide, flat, thin protrusion at the front of the cell, known as the lamellipodium, as shown in figure 1(a). The lamellipodium is an actin rich ∼100 nm thick protrusion containing a highly branched network of actin filaments [13, 14]. The front of the lamellipodium, known as the leading edge of the cell, is thought to protrude due to forces generated by actin polymerisation, described by the ‘Brownian ratchet’ model [15, 16]. The energy input driving the system out of equilibrium is provided by the hydrolysis of ATP, which is required for the binding of actin subunits. Actin filaments, fixed at the back by adhesion to the substrate, polymerise against the leading edge pushing the membrane forward. Adhesion with the substrate at the back of the cell is then broken, allowing the back of the cell to move forward to follow the leading edge. Although cell crawling can occur without functional myosin [17], actomyosin contraction usually plays an important, and sometimes dominant, role.

Actomyosin contraction is caused by clusters of myosin II molecular motors (minifilaments) interacting with actin filaments. Myosin ‘walks’ along actin filaments towards the barbed (plus) end. Within actin bundles or networks, clusters of myosin can bind to more than one actin filament at the same time. If these two actin filaments have different directions, motors attempting to walk in different directions will exert stress on the filaments, which in the case of actomyosin is contractile. Various models have been proposed for how this contraction is generated at the microscopic level [18–21]. At a cellular scale, continuum descriptions of actomyosin have been successfully developed in particular the theory of active gels [22–24]. Active matter is material that is out of equilibrium due to energy input at the level of the constituent elements. In the case of actomyosin these elements are actin filaments and molecular motors and the energy input is biochemical energy from ATP binding and hydrolysis, required for the action of myosin. We refer readers to recent reviews [25–27] for more details of this formalism.

There are clear differences between cells migrating on a flat stiff substrate and those in vivo or embedded in gels made of extracellular matrix proteins such as collagen [28], see figure 1(b). Substrate rigidity, adhesion and confinement profoundly alter cell migration mechanisms [29–32]. In confinement cells can switch to a different motility mode, often called ‘amoeboid’, in which actomyosin contraction at the rear of the cell induces a flow of actin cortex towards the back of the cell. Due to friction with the confined environment this retrograde flow propels the cell forward [33–37]. Highly contractile cells form blebs, which are outward bulges of the membrane that are devoid of actin. It is thought that cells migrating in matrices bleb through constrictions into available space and, if blebs are prevented from retracting due to the matrix fibres, polarised motion can ensue [38]. For cells migrating through small constrictions in matrices or within microchannels the nucleus can get stuck. Since the nucleus is harder to deform than the rest of the cell, the nucleus is the rate limiting step for cells to get through constrictions that are smaller than the unconfined nucleus size (in channels, matrices or in vivo).
Figure 2. Cartoon showing a nucleus. The nuclear envelope, represented by a double black/mauve bilayer, is supported by the lamina represented in green. The nuclear envelope is punctuated by several transmembrane proteins such as the nuclear pores (in orange) and the LINC complex, made up of a SUN-domain protein (green) and a KASH-domain (yellow). The LINC complex mechanically connects the lamina to the cytoskeleton. DNA inside the nucleus is represented by blue curved lines.

[39–41]. Myosin appears to be important in generating the force required to get the nucleus through small spaces [42]. To find out how the nucleus is deformed and how it affects cell motility, we need to consider the mechanical properties of the nucleus as well as how the nucleus is linked to the cytoskeleton and the cytoskeleton to the extracellular matrix. In the next section, we therefore consider the mechanical properties of the nucleus.

3. Mechanical properties of the nucleus

Sufficient nuclear stiffness is required for migration in three dimensional environments [2] and nucleus deformability is necessary when cells are squeezing through small constrictions [39]. In this section we introduce the nucleus and discuss its mechanical properties, which are relevant to cell motility.

In eukaryotic cells, the nucleus contains the chromatin (DNA and associated proteins). It is the largest organelle, occupying a sizeable fraction of the total cell volume. The nucleus is delimited by the nuclear envelope, which consists of two concentric membranes, as shown in figure 2. The nuclear membrane contains nuclear pores, which actively transport selected molecules. It also contains a wide range of other transmembrane proteins such as the LINC complexes, which mechanically connect the cytoskeleton to the nucleoskeleton.

Inside the nucleus the nuclear membrane is supported by the lamina, a thin (∼ 100 nm) network of intermediate filaments making up the nucleoskeleton [13]. This network mainly consists of intermediate filaments called lamins (type A, B, and C). Lamins are thought to modify chromatin organisation and, crucially to our discussion, are considered to give the nucleus its mechanical stiffness [43].

In healthy cells, the nucleus is typically an order of magnitude stiffer than the cell cytoskeleton [39] and on timescales relevant to cell migration (minutes [4]) appears to be elastic since it regains its original shape after deformation within seconds of force removal [44]. The stiffness of the nuclear lamina has been measured by micropipette aspiration of isolated Xenopus oocyte nuclei with and without the majority of chromatin (removed by swelling) [45]. Swelled and unswelled nuclei give similar values for the extensional elastic modulus of ∼ 25 mN m⁻¹. The nuclear lamina appears to break beyond a deformation threshold confinement [46]. Lamina A and C are thought to provide the rigidity of the nucleus since cells lacking lamins A and C have more deformable nuclei, whereas lamina B only has a minor effect on nuclear stiffness [47, 48]. This agrees with the result [49] that the relaxation time increases with lamina A to B ratio (i.e. increasingly elastic behaviour for a constant measurement time), although not with authors’ interpretation of the relative roles of lamins A and B. Consistent with the view that lamina A provides nuclear stiffness, increased lamina A levels lead to less deformable nuclei and reduced cell migration through small pores [50]. On the other hand, cells with decreased levels of lamina A have fragile nuclei that rupture frequently [51]. Mutations in lamins cause many diseases known collectively as laminopathies e.g. muscular dystrophy. For a review on the role of lamins and nuclear mechanics in disease see [51].

Lamins therefore play a key role in the mechanical properties of the nucleus directly through the lamina properties itself but also indirectly via interactions with chromatin [47]. For example, stress exerted on embryonic stem cells has been shown to induce chromatin decondensation associated with auxetic (negative Poisson ratio) behaviour of the nucleus [52], i.e. on stretching the nucleus expands in the direction perpendicular to the stretch direction. Interestingly, assuming interactions between lamins and chromatin affect nuclear mechanical properties, this coupling could also play a crucial role in mechanotransduction by influencing gene expression in response to mechanical forces [47]. The nucleus is often assumed to be mechanically passive (unlike the active cytoskeleton). However, the nuclear lamina itself can respond biochemically to the mechanical environment by upregulating lamin A on stiff substrates and phosphorylating lamins (promoting disassembly) on soft substrates [53] (see also section 4.3).

The contents of the nucleus also contribute to its mechanical properties. Isolated chromosomes respond elastically but inside the nucleus they can flow depending on how much they are tethered to the nuclear periphery [54]. Schreiner et al [54] use isolated S. pombe nuclei, which lack lamins, to isolate the mechanical effect of chromatin. Using optical tweezers they find that these nuclei are elastic with a minor viscous component, but nuclei with untethered chromosomes are highly deformable, with shorter relaxation times, lower stiffness and viscosity. Stem cells, which do not express lamin A/C, are much less stiff than differentiated cells and show irreversible nuclear deformation characteristic of plasticity [55]. Pajerowski et al [55] find chromatin is stiff when condensed by cations but flows otherwise. Using micropipette experiments with GFP labelling in epithelial cells, they find the lamina is stretched whereas chromatin flows.
For a more detailed review of the mechanical properties of the nucleus we refer readers to [51, 56, 57].

4. Nucleus-cytoskeleton-extracellular matrix connections

4.1. Nucleus-cytoskeleton connections

The role of the nucleus in cell migration is clearly dependent on the connections between the nucleus and the motility generating components of the cytoskeleton. Interactions between the nucleus and the cytoskeleton are mediated by LINC (Linker of Nucleoskeleton and Cytoskeleton) complexes [58], as depicted in figure 3. LINC complexes are known to be important in transmitting mechanical stresses from the cytoskeleton to the inside of the nucleus during many cell processes such as migration [59–61]. The LINC complexes are composed of two transmembrane protein families, SUN domain proteins (Sad1 and Unc-83) at the inner nuclear membrane and nesprins (nuclear envelope spectrin repeat proteins) terminated by KASH domains (Klarsicht, Anc1, and Syne Homology) at the outer nuclear membrane [62, 63]. SUN domain proteins bind to nuclear lamina [64] and interact with nuclear pore proteins, and other nuclear envelope proteins such as Samp1 [65]. Nesprins can bind to all major cytoskeletal filament networks, including actin filaments, intermediate filaments, and microtubules [66]. Nuclear deformations induced by a microneedle pulling on the cytoskeleton, are significantly reduced in cells with disrupted LINC complexes [62]. The fact that LINC complexes connect the cytoskeleton to the lamina is further demonstrated by experiments showing that a lack of functional LINC complexes results in a loss of mechanical stiffness in fibroblasts similar to that seen in lamin A depleted cells (see section 3 for discussion of lamins) [67].

The actin network is attached to the nucleus by the actin-binding domain of the giant isoforms of nesprin-1 and nesprin-2. These nesprin proteins, along with their interactions with intermediate filaments via nesprin-3, may form a scaffold around the nucleus and confine the size of the nucleus [68]. Nuclei can be moved around within the cell by KASH proteins connecting them to moving actin filaments (see section 5.1).

Microtubules are attached to the nucleus via kinesin and dynein motor proteins binding to various KASH proteins [69]. These molecular motors can move nuclei along microtubules in different directions (kinesin towards the plus end and dynein towards the minus end) [69]. For more details on the role of microtubules in moving nuclei see section 5.1.
More detailed reviews on the LINC complex and its interactions can be found in [70].

4.2. Cell adhesion

Interactions between cells and their external environment have a strong influence on cell migration, affecting not only cell speed, polarisation direction and persistence, but also what motility mechanism is used. For example, specific adhesion to the substrate is essential for cell migration on a 2D substrate but not for migration in vivo, matrices or channels [30]. The role of the nucleus in cell migration is also affected by interactions with the environment. For example, cells migrating in soft matrices are reliant on lamin A/C and LINC complexes to migrate but those on stiff 2D substrates are not [2]. This indicates the importance of the effect of the external environment on the role of the nucleus in migration. In this section we consider interactions with the external environment and provide a brief introduction to the field of cell adhesion. We refer readers elsewhere for more detailed reviews on adhesion [6, 7] and the physical extracellular environment [71].

Cell adhesion is mediated by transmembrane proteins. There exists a wide range of adhesion molecules including integrins, cadherins and selectins [72]. Cell–cell adhesions in anchoring junctions are mediated by cadherins. Cell adhesion to the extracellular matrix on the other hand, is usually mediated by integrins. Finally, selectins bind to carbohydrates or sugars.

Migrating cells can follow gradients in substrate stiffness ( durotaxis). This mechanosensitive response is mediated by adhesion sites called focal adhesions connected to the cytoskeleton [73]. For cells on a 2D substrate, microclusters of activated integrins bind to the extracellular matrix at the basal surface of the lamellipodia or filopodia at the cell periphery [74, 75]. Over time, adapter proteins talin and paxillin are recruited to integrin clusters to form nascent adhesions, some of which mature into focal adhesions, which are more stably associated with the extracellular matrix. Maturation of focal adhesions occurs concomitantly with the formation of contractile actin bundles called stress fibres. Focal adhesions increase in size and become elongated in the stress fibre direction [75, 76]. Radial stress fibres (perpendicular to the leading edge) are anchored at one end to a focal adhesion, whereas transverse arcs of actin bundles (parallel to the leading edge) are anchored at one end to a focal adhesion, whereas transverse arcs of actin bundles (parallel to the leading edge) are anchored at one end to a focal adhesion, whereas

4.3. Mechanosensitivity and mechanotransduction

Cells are able to detect and respond to mechanical forces and environmental stiffness. This is important in cell migration, for example for cells undergoing durotaxis [5, 73]. Mechanosensitive proteins can sense mechanical changes and react to them. For example, stretching the adhesion protein talin exposes a vinculin binding site, and subsequently, leads to vinculin binding [90]. Several adhesion and cytoskeletal proteins, including integrin and myosin, have been found to exhibit increased affinity to their ligands under mechanical stress [91]. For more details on the interplay between adhesion proteins and actin in mechanosensing and mechanotransduction we refer readers to [6]. In addition to adhesion proteins, many ion channels (transmembrane proteins forming pores controlling ion transport) in both the cell membrane and nuclear membrane are mechanosensitive. Stretch activated ion channels open in response to membrane tension, transporting ions such as calcium across the membrane [92].

Mechanotransduction refers to the conversion of an external mechanical force signal to biochemical responses and gene expression. For example, Iyer et al [93] observe decondensation of chromatin and nuclear entry of the transcription factor MKL following force application by magnetic beads adhered to the cell membrane. As already mentioned in section 3, the nuclear lamina itself responds biochemically to the mechanical environment with lamin A upregulated on stiff substrates and phosphorylated (promoting disassembly as occurs prior to cell division) on soft substrates [53].

It is clear then that nuclear–cytoskeleton connections combined with adhesion to the external environment mediate the transduction of forces to the nucleus. Such mechanotransduction is key to the role of the nucleus in many cell processes, including in cell migration. Having briefly reviewed the mechanisms of cell motility, the mechanical properties of the nucleus and nucleus-cytoskeleton-extracellular environment
connections we next draw these aspects together to consider some particular roles of the nucleus in migrating cells.

5. Physical roles of the nucleus in migrating cells

5.1. Nuclear positioning and cell polarisation

Cell migration direction is given by the polarisation of the cell and the position of the nucleus within the cell correlates with this, usually being positioned towards the rear [66]. Cell polarisation or polarity is the morphological asymmetry of cells, often associated with a functional asymmetry such as cell motility. For cells migrating on 2D substrates the nucleus is generally positioned behind the centrosome (also known as the microtubule organising centre, MTOC) as shown in figure 4. However, some cells migrating in geometric confinement and in vivo have the centrosome behind the nucleus. For example, Pouthas et al [94] find that cells that migrate on 2D substrates with the centrosome in front of the nucleus, migrate on thin fibronectin adhesive lines with the centrosome behind the nucleus. Similarly, fibroblasts migrating in 1D and 3D have the centrosome at the back, behind the nucleus [95]. Thiéry et al [96] showed using micropatterned substrates that anisotropy of the adhesive microenvironment directs polarity. They found the centrosome is always near the cell centroid and the nucleus is off centre towards lower adhesion contractile cell edges. The polarised microtubule network helps maintain cell polarisation and consequently promotes persistent migration. This is thought to be due to polarised trafficking of migration related molecules along microtubules [97]. The mechanisms regulating the orientation of the centrosome relative to the nucleus are thus relevant to cell migration direction and persistence.

Nucleus positioning is the result of interactions with actin, microtubules and intermediate filaments [66, 98–100]. As explained in section 4.1, these interactions are mediated by nesprins that connect the nucleus to actin, motor proteins and intermediate filaments. Molecular motors such as dynein moving on microtubules may exert active forces on the nucleus [100]. Microtubules appear to have a particularly important role in nuclear positioning and nuclear movement, for example, in migrating neuronal cells [66]. Lamins are also important for cell polarisation, as seen from the fact that lamin A/C deficient cells are unable to correctly polarise [101]. Nuclear position cannot be considered independent from centrosomal positioning since there is a physical link between the nucleus and the centrosome via kinesin and dyneins [102]. Dynein molecular motors at the cell periphery pulling on microtubules are key to centrosome positioning [103].

Actin also plays a role in nuclear positioning. For example, rearward nuclear movement in migrating fibroblast cells is dependent on actin, nesprin and SUN proteins, known as transmembrane actin-associated nuclear (TAN) lines [104]. As discussed in section 4.1, the nucleus is connected to actin and therefore when there is an actin retrograde flow the nucleus is transported backwards with it. It has also been suggested that actomyosin contraction at the back could push the nucleus forwards and actomyosin contraction at the front could pull the nucleus forwards [105].

Changes in migration direction sometimes involve nuclear rotation to reorient the polarisation axis with the nucleus behind the centrosome. Nuclear rotation has been observed in various conditions, and appears to depend on dynein activity [100, 106, 107]. This may be due to tension between the centrosome and the nucleus generated by dynein walking along microtubules [100]. Many cell types display alternating phases of fast persistent migration and slow persistent movement. Fast persistent migration correlates with an intact actin cap whereas changes in migration direction may be due to dynein driven nuclear rotation whilst the actin cap transiently disappears [84, 108]. Alternatively actomyosin contractility may explain nuclear rotation with the nucleus entering only as a passive inclusion [25, 109, 110]. Micropatterns of adhesive stripes promote persistent migration, actin cap formation and elongated nuclei whereas cells on circular micropatterns are non-motile and display dynein-driven rotation of their rounded nuclei [84]. Cells migrating along synthetic nanofibres also show a correlation between nuclear elongation and cell velocity and persistence [85]. As discussed in section 4.2, it is thought that actin bundles in elongated cells compress the nucleus, causing nuclear elongation [84, 87, 111]. Since stress fibers are connected to the extra cellular matrix, nucleus elongation and cell polarisation are influenced by the external conditions. Several experiments using micropatterns show that changes in local adhesion affect orientational ordering of stress fibres across the whole cell, suggesting cells can integrate local mechanical cues at the whole cell level [87, 96, 112].

5.2. Nucleus-cytoskeleton connection dependent migration

As discussed in section 5.1, the position of the nucleus is important in cell polarisation, which sets the direction of motion. In addition to this, experiments have found that the nucleus plays an important role in the motion of migrating cells [2]. Nucleus-cytoskeleton connections appear to be required for migration in soft 3D matrices mimicking tissue environments. Lamin A/C deficient cells are able to migrate on a collagen coated 2D glass substrate but when embedded in a 3D collagen matrix their speed is significantly lower than...
wild type cells. The same effect is observed when LINC complexes or nesprins are disrupted. This implies that the rigidity of the nucleus and nucleus-cytoskeleton connections are important for migration within collagen matrices but less so on flat glass substrates. However, from these experiments it is not clear to what extent this effect is due to the difference in rigidity of the environment or the difference in confinement geometry.

The integrity of the nucleus and nucleus-cytoskeleton connections also have an effect on cell migration on 2D substrates. Lamin A/C deficient cells in wound healing assays have significantly reduced migration speed [101]. Similarly, nesprin-1 depleted endothelial cells migrate more slowly [113]. Nesprin-1 depletion results in increased focal adhesion assembly, cell traction and nuclear height, whilst migration speed is decreased. Inhibiting myosin results in a similar increase in the height of nuclei. Therefore Chancellor et al [113] suggest that the nucleus balances tension due to actomyosin but that without nesprin-1 this tension is balanced by the substrate.

5.3. Cell squeezing through constrictions

In recent decades there have been many studies of cell migration in various confined environments. Examples include adhesive micropatterning [114], 1D migration along synthetic nanofibres [85], 2D confinement [46], microfabricated microchannels [115], micropillars [116, 117], invasion into gels [118], embedding in matrices such as collagen [28, 30, 119] and in vivo studies [119]. Many of these techniques are reviewed in [31]. Here we do not provide a detailed review of this body of work but instead consider some examples which have specifically looked at the nucleus.

Microfabrication techniques have enabled the study of cells moving between micropillars, in channels and through constrictions of controlled geometry without being driven by flow [31, 117] (see figure 5). Microfluidics methods that do impose flow (deformability cytometry) are also used to study cell deformations and stiffness [120]. The dynamics of the nucleus is the rate limiting factor for cells squeezing through constrictions [39, 40]. In order for cells to get through constrictions that are smaller than the size of the nucleus, the nucleus must deform. In normal cells the nucleus is more difficult to deform than the rest of the cell, however, lamin A/C deficient cells have more deformable nuclei [121]. Cancer cells, often associated with lamina mutations, have softer nuclei and consequently appear to get through smaller constrictions more easily [39]. The mechanisms for how the cell generates the forces required to deform the nucleus are not yet well understood. It is not yet clear whether the nucleus is pushed or pulled through constrictions. It appears that more adherent cells may pull the nucleus and less adherent cells push the nucleus [28].

5.4. Models of the nucleus during cell migration

The nucleus is often ignored in models of cell motility, since it is assumed to be passive and not the driving force for motion. However, as we have pointed out in this article, the nucleus does have an important role in cell migration. Here we mention some of the theoretical studies that do consider the nucleus.

Sometimes the nucleus is not modelled explicitly but its presence is included implicitly simply as a passive load with corresponding frictional drag, for example as suggested by [35]. To model the nucleus explicitly, the simplest model is to treat the nucleus as a deformable linearly elastic sphere (linear elastomer), as in [123] who calculate the maximum deformation of the nucleus at a bottleneck in a quasi one dimensional model. Givens C et al [124] calculate the energy required to deform the nucleus from an initial spherical shape to an ellipse or a cigar shape in order for it to fit into a cylindrical channel. They consider two models for the nucleus; one as a liquid droplet surrounded by an elastic shell and the second as an incompressible elastic solid. Another continuum model for the nucleus has been used by [125] who model the nucleus as an encapsulated liquid drop. The nucleus and cell are modelled as Newtonian fluids surrounded by elastic interfaces which are simulated using the immersed boundary method.

A more engineering approach is used by [126] who use a finite element method to model the cytoplasm and nucleus in a two dimensional simulation. They model the nucleus as a viscoelastic material described by the Maxwell model, surrounded by an elastic circle representing the lamina. Agent based models have also been used such as the cellular Potts model [127] which uses a Metropolis Monte Carlo method to stochastically simulate a lattice based model of cells and nuclei with a given energy cost to deforming their shape. Combining these different modelling approaches together has also been attempted such as the hybrid agent-based finite element model for cell motility in [128].

In the future analytical and numerical studies including the nucleus should help analyse experimental data and contribute to deducing the role of the nucleus in cell migration [129, 130].

6. Outlook

We have given an overview of cell motility mechanisms and have reviewed some of the known mechanical properties of the nucleus, its coupling to the cytoskeleton and indirectly to the extracellular matrix. In particular, we have discussed the organisation of the actin cytoskeleton and its coupling to the nucleus and the extracellular matrix. However, the role played
by microtubules in cell migration is less clear. Although we know about microtubule coupling to the nucleus, their coupling to the extracellular matrix and the coupling between the centrosome and the nucleus remain poorly understood. The role of microtubules in cell migration has not been as well studied and may be more important than previously thought [131]. Whilst it is clear microtubules are important in cell polarisation, it is not clear whether the position of the centrosome is a cause or an effect of cell polarisation.

The nucleus needs to deform for cells to migrate through small constrictions. However, what is the mechanism or mechanisms by which cells push or pull the nucleus through small constrictions? This is not yet clearly understood.

In the field of mechanotransduction, there are many questions remaining regarding how gene expression is affected by mechanics. How does mechanotransduction of forces transmitted from the external environment to the nucleus affect gene expression? We are still a long way from fully explaining mechanotransduction.

Much is known on a microscopic level but questions remain in integrating this knowledge at the cellular scale. From a material physics perspective, how does the presence of the nucleus affect cell migration? Treating the nucleus as a passive inclusion with excluded volume, how does the cytoskeleton flow around it? How does the nucleus constrain cytoskeleton dynamics?

Finally there is much still to be learnt about the effects of physical properties of nuclei in disease and how this relates to cell migration, for example in metastatic cancer cells. Discerning this may lead to new approaches to the development of therapies in the future.

There remains much to be discovered to fully understand the physical roles of the nucleus in cell migration.

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References

[1] Verkhovsky A B, Svitkina T M and Borisy G G 1999 Self-polarization and directional motility of cytoplasm Curr. Biol. 9 11–20
[2] Khatua S B et al 2012 The distinct roles of the nucleus and nucleus-cytoskeleton connections in three-dimensional cell migration Sci. Rep. 2 488
[3] Fletcher D A and Theriot J A 2004 An introduction to cell motility for the physical scientist Phys. Biol. 1 T1–10
[4] Mairui P et al and WCR participants 2012 The first world cell race Curr. Biol. 22 R673–5
[5] Lo C M, Wang H B, Dembo M and Wang Y L 2000 Cell movement is guided by the rigidity of the substrate Biophys. J. 79 144–52
[6] Schwarz U S and Gardel M L 2012 United we stand—integrating the actin cytoskeleton and cell—matrix adhesions in cellular mechanotransduction J. Cell Sci. 125 3051–60
[7] Humphries J D, Paul N R, Humphries M J and Morgan M R 2015 Emerging properties of adhesion complexes: what are they and what do they do? Trends Cell Biol. 25 388–97
[8] Wolfenson H, Iskratsch T and Sheetz M P 2014 Early events in cell spreading as a model for quantitative analysis of biomechanical events Biophys. J. 107 2508–14
[9] Woodham E F and Machelsky L M 2014 Polarised cell migration: intrinsic and extrinsic drivers Curr. Opin. Cell Biol. 30 25–32
[10] Goehring N W and Grill S W 2013 Cell polarity: mechaanochemical patterning Trends Cell Biol. 23 72–80
[11] Swaney K F, Huang C-H and DeVreotes P N 2010 Eukaryotic chemotaxis: a network of signaling pathways controls motility, directional sensing, and polarity Annu. Rev. Biophys. 39 265–89
[12] Huber F, Boire A, López M P and Koenderink G H 2015 Cytoskeletal crosstalk: when three different personalities team up Curr. Opin. Cell Biol. 32 39–47
[13] Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K and Walter P 2014 Molecular Biology of the Cell 6th edn (New York: Garland Science)
[14] Pollard T D and Borisy G G 2003 Cellular motility driven by assembly and disassembly of actin filaments Cell 112 453–65
[15] Peskin C S, Odell G M and Oster G F 1993 Cellular motions and thermal fluctuations: the brownian ratchet Biophys. J. 65 316–24
[16] Mogilner A 2006 On the edge: modeling protrusion Curr. Opin. Cell Biol. 18 32–9
[17] Bray D 2001 Cell Movements: from Molecules to Motility (New York: Garland Science)
[18] Kruse K and Jülicher F 2000 Actively contracting bundles of polar filaments Phys. Rev. Lett. 85 1778–81
[19] Liverpool T B, Marchetti M C, Joanny J F and Prost J 2009 Mechanical response of active gels Europhys. Lett. 85 18007
[20] Hawkins R J and Liverpool T B 2014 Stress reorganisation and response in active solids Phys. Rev. Lett. 113 028102
[21] Lenz M, Thoresen T, Gardel M L and Dinner A R 2012 Contractile units in disordered actomyosin bundles arise from f-actin buckling Phys. Rev. Lett. 108 238107
[22] Kruse K, Joanny J F, Jülicher F, Prost J and Sekimoto K 2004 Axsters, vortices, and rotating spirals in active gels of polar filaments Phys. Rev. Lett. 92 078101
[23] Kruse K, Joanny J F, Jülicher F, Prost J and Sekimoto K 2005 Generic theory of active polar gels: a paradigm for cytoskeletal dynamics Eur. Phys. J. E: Soft Matter 16 5–16
[24] Kruse K, Joanny J F, Jülicher F and Prost J 2006 Contractility and retrograde flow in lamellipodium motion Phys. Biol. 3 130–7
[25] Marchetti M C, Joanny J F, Ramaswamy S, Liverpool T B, Prost J, Rao M and Simha R A 2013 Hydrodynamics of soft active matter Rev. Mod. Phys. 85 1143
[26] Ramaswamy S 2010 The mechanics and statistics of active matter Annu. Rev. Condens. Matter Phys. 1 323–45
[27] Jülicher F, Kruse K, Prost J and Joanny J F 2007 Active behavior of the cytoskeleton Phys. Rep. 449 3–28
[28] Petrie R J and Yamada K M 2015 Fibroblasts lead the way: a unified view of 3d cell motility Trends Cell Biol. 25 666–74
[29] Engler A J, Sen S, Lee Sweeney H and Discher D E 2006 Matrix elasticity directs stem cell lineage specification Cell 126 677–89
[30] Lämmermann T et al 2008 Rapid leukocyte migration by integrin-independent flowing and squeezing Nature 453 51–5
[31] Lautenschläger F and Piel M 2013 Microfabricated devices for cell biology: all for one and one for all Curr. Opin. Cell Biol. 25 116–24
Chambliss A B, Khatau S B, Erdenberger N, Robinson D K, Kim D-H, Khatau S B, Feng Y, Walcott S, Sun S X, Kim D-H, Chambliss A B and Wirtz D 2013 The multi-faceted
Kim D-H, Cho S and Wirtz D 2014 Tight coupling between
Linder S 2007 The matrix corroded: podosomes and
Fraley S I, Feng Y, Krishnamurthy R, Kim D-H, Celedon A, è Renkawitz J, Schumann K, Weber M, L Burnette D T, Manley S, Sengupta P, Sougrat R, Gardel M L, Schneider I C, Aratyn-Schaus Y and
Alexandrova A Y, Arnold K, Schaub S, Vasiliev J M, Choi C K, Vicente-Manzanares M, Zareno J, Whitmore L A, 22
Ridley A J 2011 Life at the leading edge –
323
41
Science
talin rod molecules activates vinculin binding Science 323 638–41

[91] Veigel C, Molloy J E, Schmitz S and Kendrick-Jones J 2003 Load-dependent kinetics of force production by smooth muscle myosin measured with optical tweezers Nat. Cell Biol. 5 980–6

[92] Ingber D E 2006 Cellular mechanotransduction: putting all the pieces together again FASEB J. 20 811–27

[93] Venkatases Iyer K, Pulford S, Mogilner A and Shivashankar G V 2012 Mechanical activation of cells induces chromatin remodeling preceding MK1 nuclear transport Biophys. J. 103 1416–28

[94] Pouthas F, Girard P, Lecaudey V, Ly T B N, Gilmore D, Boulin C, Pepperkok R and Reynaud E G 2008 In migrating cells, the golgi complex and the position of the centrosome depend on geometrical constraints of the substratum J. Cell Sci. 121 2406–14

[95] Doyle A D, Wang F W, Matsumoto K and Yamada K M 2009 One-dimensional topography underlies three-dimensional fibrillar cell migration J. Cell Biol. 184 481–90

[96] Théry M, Racine V, Piel M, Pépin A, Dimitrov A, Chen Y, Sibarita J-B and Bornens M 2006 Anisotropy of cell adhensive microenvironment governs cell internal organization and orientation of polarity Proc. Natl Acad. Sci. USA 103 19771–6

[97] Etienne-Manneville S 2013 Microtubules in cell migration Annu. Rev. Cell Dev. Biol. 29 471–99

[98] Starr D A 2009 A nuclear-envelope bridge positions nuclei and moves chromosomes J. Cell Sci. 122 577–86

[99] Tsai J-W, Bremner K H and Valle B R 2007 Dual subcellular roles for lls1 and dynein in radial neuronal migration in live brain tissue Nat. Neurosci. 10 970–9

[100] Wu J, Lee K C, Dickinson R B and Lele T P 2011 How dynein and microtubules rotate the nucleus J. Cell. Physiol. 226 2666–74

[101] Lee J S H, Hale C M, Panorchan P, Khatau S B, George J P, Tseng Y, Stewart C L, Hodzic D and Wirtz D 2007 Nuclear lamin a/c deficiency induces defects in cell mechanics, polarization, and migration Biophys. J. 93 2542–52

[102] Fridolfsson H N, Ly N, Meyerzon M and Starr D A 2010 Unc-83 coordinates kinesin-1 and dynein activities at the nuclear envelope during nuclear migration Dev. Biol. 338 237–50

[103] Elric J and Etienne-Manneville S 2014 Centrosome positioning in polarized cells: common themes and variations Exp. Cell Res. 328 240–8

[104] Lugo G W G, Gomes E R, Folker E S, Vintinner E and Gundersen G G 2010 Linear arrays of nuclear envelope proteins harness retrograde actin flow for nuclear movement Science 329 956–9

[105] Wu J, Kent I A, Shekar N, Chancellor T J, Mendonca A, Dickinson R B and Lele T P 2014 Actomyosin pulls to advance the nucleus in a migrating tissue cell Biophys. J. 106 7–15

[106] Geraschenko M V, Chernovivanenko I S, Moldaver M V and Minin A A 2009 Dynein is a motor for nuclear rotation while vimentin IFs is a ‘brake’ Cell Biol. Int. 33 1057–64

[107] Levy J R and Holzbaur E L F 2008 Dynin drives nuclear rotation during forward progression of motile fibroblasts J. Cell Sci. 121 3187–95

[108] Razafa Y, Wirtz D and Hodzic D 2014 Nuclear envelope in nuclear positioning and cell migration Adv. Exp. Med. Biol. 773 471–90

[109] Kumar A, Maitra A, Sumit M, Ramaswamy S and Shivashankar G V 2014 Actomyosin contractility rotates the cell nucleus Sci. Rep. 4 3781

[110] Gomes E R, Jari S and Gundersen G G 2005 Nuclear movement regulated by Cdc42, MRCK, myosin, and actin flow establishes MTÖC polarization in migrating cells Cell 121 451–63
[111] Versaevel M, Grevesse T and Gabriele S 2012 Spatial coordination between cell and nuclear shape within micropatterned endothelial cells Nat. Commun. 3 671

[112] Mandal K, Wang I, Vitelli E, Orellana A C and Ballard M 2014 Cell dipole behaviour revealed by ECM sub-cellular geometry Nat. Commun. 5 5749

[113] Chancellor T J, Lee J, Thodeti C K and Lele T 2010 Actomyosin tension exerted on the nucleus through nesprin-1 connections influences endothelial cell adhesion, migration, and cyclic strain-induced reorientation Biophys. J. 99 218–23

[114] Théry M 2010 Micropatterning as a tool to decipher cell morphogenesis and functions J. Cell Sci. 123 4201–13

[115] Heuzé M L, Collin O, Terriac E, Lennon-Duménil A-M and Piel M 2011 Cell migration in confinement: a micro-channel-based assay Methods Mol. Biol. 769 415–34

[116] Saez A, Ghibaudo M, Buguin A, Silberzan P and Ladoux B 2007 Rigidity-driven growth and migration of epithelial cells on microstructured anisotropic substrates Proc. Natl Acad. Sci. USA 104 8281–6

[117] Isermann P, Davidson P M, Sliz J D and Lammerding J 2012 Unit 22.16 Assays to measure nuclear mechanics in interphase cells Curr. Protocols Cell Biol. 56:22.16:22.16.1–22.16.21

[118] Koch T M, Münster S, Bonakdar N, Butler J P and Fabry B 2012 3d traction forces in cancer cell invasion PLoS One 7 e33476

[119] Wolf K, Alexander S, Schacht V, Coussens L M, von Andrian U H, van Rheenen J, Deryugina E and Friedl P 2009 Collagen-based cell migration models in vitro and in vivo Semin. Cell Dev. Biol. 20 931–41

[120] Otto O et al 2015 Real-time deformability cytometry: on-the-fly cell mechanical phenotyping Nat. Methods 12 199–202 (4 p following 202)

[121] Lammerding J, Christian Schulze P, Takahashi T, Kozlov S, Sullivan T, Kamm R D, Stewart C L and Lee R T 2004 Lamin a/c deficiency causes defective nuclear mechanics and mechanotransduction J. Clin. Invest. 113 370–8

[122] Thiam H R et al 2016 Perinuclear ARP2/3-driven actin polymerization enables strong nuclear deformation to facilitate cell migration through complex environments Nat. Commun. 7 10997

[123] Le Berre M, Liu Y-J, Hu J, Mauri P, Bénilchou O, Voituriez R, Chen Y and Piel M 2013 Geometric friction directs cell migration Phys. Rev. Lett. 111 198101

[124] Giverso C, Grillo A and Preziosi L 2014 Influence of nucleus deformability on cell entry into cylindrical structures Biomech. Modelling Mechanobiol. 13 481–502

[125] Leong F Y, Li Q, Lim C T and Chiam K-H 2011 Modeling cell entry into a micro-channel Biomech. Modelling Mechanobiol. 10 755–66

[126] Aubry D, Thiam H, Piel M and Allena R 2015 A computational mechanics approach to assess the link between cell morphology and forces during confined migration Biomech. Modelling Mechanobiol. 14 143–57

[127] Scianna M and Preziosi L 2013 Modeling the influence of nucleus elasticity on cell invasion in fiber networks and microchannels J. Theor. Biol. 317 394–406

[128] Tozluoğlu M, Tournier A L, Jenkins R P, Hooper S, Bates P A and Sahai E 2013 Matrix geometry determines optimal cancer cell migration strategy and modulates response to interventions Nat. Cell Biol. 15 751–62

[129] Estabrook I D, Thiam H R, Piel M and Hawkins R J 2016 Nuclear deformation during cell migration through constrictions (in preparation)

[130] Fruleux A and Hawkins R 2016 in preparation

[131] Balzer E M, Tong Z, Paul C D, Hung W-C, Stroka K M, Boggs A E, Martin S S and Konstantopoulos K 2012 Physical confinement alters tumor cell adhesion and migration phenotypes FASEB J. 26 4045–56