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Review Article

Diverse roles of non-muscle myosin II contractility in 3D cell migration

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All is flux, nothing stays still. Heraclitus of Ephesus' characterization of the universe holds true for cells within animals and for proteins within cells. In this review, we examine the dynamics of actin and non-muscle myosin II within cells, and how their dynamics power the movement of cells within tissues. The 3D environment that migrating cells encounter along their path also changes over time, and cells can adopt various mechanisms of motility, depending on the topography, mechanics and chemical composition of their surroundings. We describe the differential spatio-temporal regulation of actin and myosin II-mediated contractility in mesenchymal, lobopodial, amoeboid, and swimming modes of cell migration. After briefly reviewing the biochemistry of myosin II, we discuss the role actomyosin contractility plays in the switch between modes of 3D migration that cells use to adapt to changing environments.

Introduction

Migration is a fundamental behavior of cells found in all multicellular organisms from sponges to vertebrates. During development, regeneration, normal physiology and disease, cells travel short or long distances, alone or in groups, to reach their destination and perform specific functions. For example, during vertebrate embryogenesis neural crest cells delaminate from the neural tube and migrate to distant locations, where they contribute to the formation of many different tissues [1]. Primordial germ cells (PGCs) undergo long range migrations in developing vertebrates and invertebrates, from their site of formation to their somatic gonadal niche [2,3]. Immune cells continuously migrate throughout the animal body searching for signs of pathogens or transformed cells, and when an injured or infected tissue sends out an inflammatory signal, many immune cells rapidly migrate to the site for repair of the damaged tissue [4–6]. Understandably, cell motility is essential for normal animal development and physiology [7,8]. Defects in cell motility have severe consequences, such as embryonic lethality, congenital malformation, vascular disorders, and neurological disease. On the flip side, when tumor cells gain the ability of locomotion cancer can metastasize and become deadly [9]. In all these cases, cells move through a 3D microenvironment interacting with the extracellular matrix (ECM), body fluids, soluble and bound growth factors, as well as other cells. How does the 3D microenvironment influence cell motility? Answering this question is technically challenging, which is why most cell migration research has traditionally focussed on mechanisms of cell motility on 2D surfaces. In recent years, a growing body of work directly addressed the role of 3D microenvironments on cell motility in a variety of models. In this review, we will describe several distinct modes of motility that cells adopt under different 3D conditions *in vitro* and *in vivo*. We will then briefly review the biochemistry of non-muscle myosin II (NMII), which is the molecular engine powering most types of cell motility. Finally, we will examine how different spatio-temporal dynamics of myosin II-based contractility drive the different modes of 3D cell migration and the role of contractility in the plasticity of 3D migration. We will end with some open questions and future prospective.

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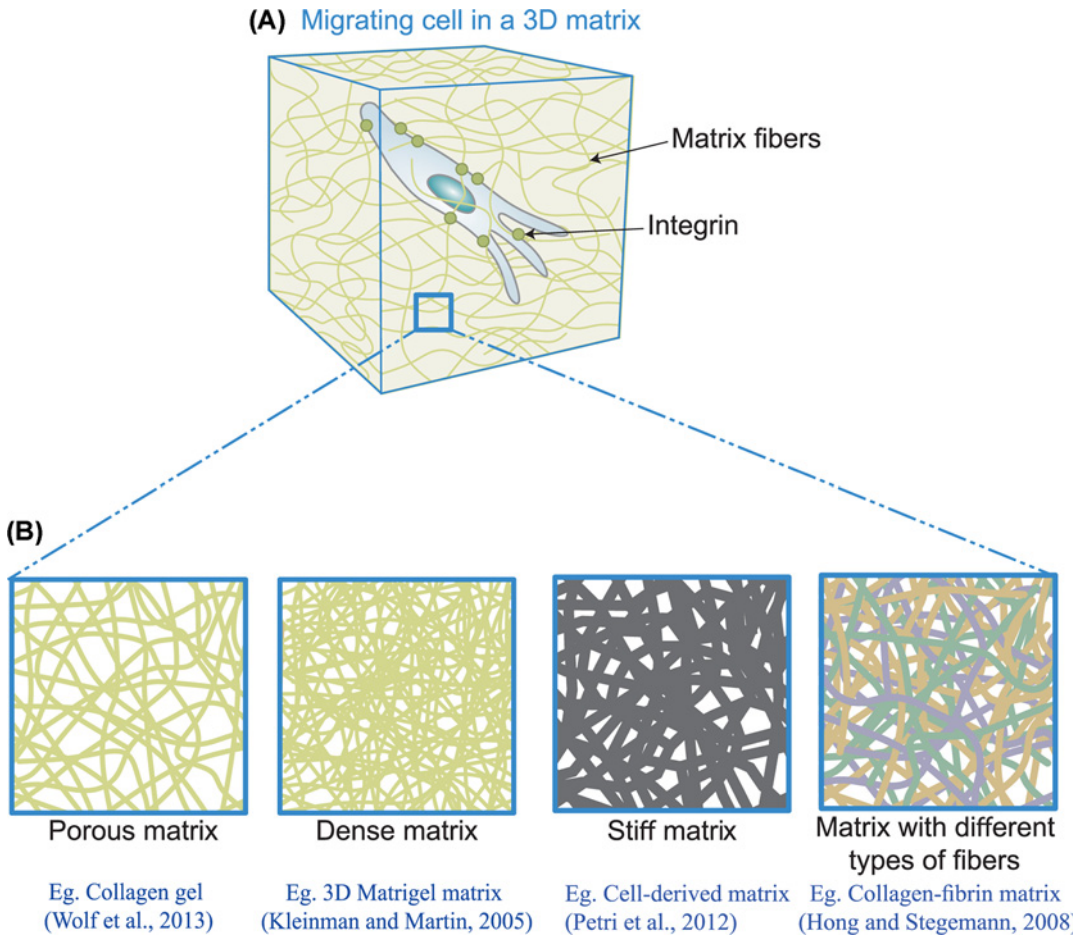


Figure 1. Different 3D matrix architectures that influence cell migration behavior.

(**A**) A mesenchymal cell migrating in a 3D matrix with cell-ECM adhesions (integrins-green) present throughout the cell body. (**B**) Matrix with different physical properties such as porosity, density, stiffness, and composition.

Modes of 3D cell migration

3D environments differ in their topography and mechanical properties as well as their chemical composition. Topography includes the density and arrangement of the ECM fibers, which impacts on the degree of confinement of cells and the pore sizes through which they need to pass. Mechanical properties such as viscoelasticity or stiffness are determined by the type of ECM proteins and the degree of their cross-linking. The chemical composition dictates the adhesive properties of the matrix and can regulate cellular signaling (Figure 1). Examples of different types of 3D matrices with their composition, stiffness, relevance to *in vivo* microenvironment and associated cell migration behavior are summarized in Table 1. How cells respond to different combinations of these variables will depend on the physical and biochemical properties of the cells themselves, which vary between cell types. The different modes of 3D migration described herein have been largely categorized on the basis of the morphology of the migrating cells and the presence or absence of discrete cell-matrix adhesions (Table 2).

Mesenchymal mode

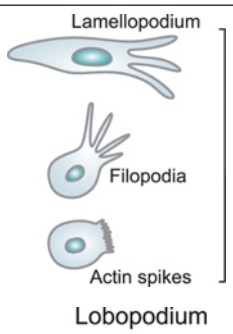
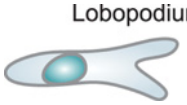
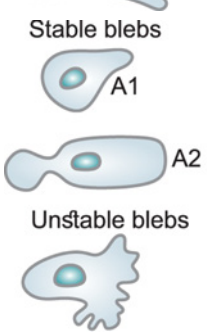
Mesenchymal mode of cell migration is characterized by actin-polymerization based protrusions such as lamellipodia, filopodia, or actin spikes [10]. Unlike the flattened morphology of mesenchymal cells migrating on a 2D surface, cells moving through the narrow spaces of 3D matrices are much more elongated, spindle-shaped, with thin protrusions emanating from the tip in all directions. Mesenchymal mode of cell motility is dependent upon integrin-mediated cell-matrix adhesions and the cell motility through interstitial space can be described as a five-step cyclic process: first, formation of actin-based protrusions at the leading edge of the cell; second, engagement of protrusion with the ECM via integrin-mediated adhesion; third, ECM cleavage and modification by cell-surface proteases known

Table 1 Examples of 3D matrices and the mode of migration they support

3D matrix	Composition	Stiffness (Pascal-Pa)	Tissue environment they mimic	Mode of cell migration	References
3D collagen gel matrix	Collagen I	2000-8500Pa	Skin tissue of embryonic mouse and adult mouse ear	Mesenchymal	[73]
Synthetic deformable elastic fibrous matrix	Electrospun dextran methacrylate fibers	1000–30,000Pa	Fibrous interstitial tissues such as fibrin-rich extracellular matrix present at wounded site and tumors with collagen fibers	Sling shot	[15]
3D matrigel	Derived from mouse sarcoma cells. Contains laminin, entactin/nidogen, collagen IV, proteoglycans, heparin sulfate, and growth factors.	450Pa	Basement membrane matrix	Amoeboid	[68]
Linear elastic cell-derived matrix	Heparan sulfate, collagen I and III, fibronectin, hyaluronic acid, proteoglycan, and thrombospondin	224–2454Pa	Soft connective tissues such as human foreskin	Lobopodial	[14]
Synthetic 3D nanofiber matrix	Electrospun polycaprolactone fibers coated with fibronectin	ND	Fibrillar tissue environment such as liver fibrosis and pulmonary fibrosis	Lobopodial	[26]

ND- Not determined

Table 2 Comparing different modes of 3D cell migration

Mode of 3D cell migration	Morphology of cells	Actomyosin contractility	Cell-matrix adhesion	Intracellular pressure	References
Mesenchymal mode		Low	High	Low	[10,12,14,15] [20–23] [24,25]
Lobopodial mode		High	High	High	[14,26,29]
Amoeboid mode		Low / High	Low	ND	[39–41] [31,32,35–38]
Swimming mode		High	NA	ND	[43,44]

NA: Not applicable; ND: Not determined.

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as membrane-tethered matrix metalloproteases (MT1-MMP) to create gaps in the interwoven dense matrix; fourth, cell contraction mediated by increased actomyosin contractility; and at last, increased tension along with the gradual disassembly of adhesion complexes at the trailing end pulls the cell in the forward direction [11–13]. This cycle is continuously repeated throughout migration. A variation to this cycle is found in cells migrating in a synthetic deformable elastic fibrous matrix with stiffness (1000–30,000 Pa) much higher than 3D collagen matrix (11–21Pa) [14,15]. Cells pull matrix fibers from the front toward the cell body, storing elastic energy. Matrix deformation is followed by a reduction of cell-ECM adhesion at the trailing end leading to sudden matrix recoil and forward translocation of the cell body. This is referred to as sling-shot cell migration [15].

A hallmark of 3D mesenchymal migrating cells is their polarization, with active cdc-42, Rac, and phosphatidylinositol (3,4,5)-trisphosphate (PIP_3) signaling at their leading-edge, where they induce lamellipodial protrusions [12]. Motility of several mesenchymal cancer cells depends upon Rac activity [16,17]. Loss of Rac or cdc-42 activity impairs melanoblast migration in the skin dermis of mice, causing aberrant pigmentation [18,19]. Besides lamellipodia, other F-actin-based protrusions, such as filopodia, plays an essential role during 3D mesenchymal cell migration. During PGC migration in the *Zebrafish* embryo, filopodia are required for chemokine-guided cell polarization [20]. Migration of endothelial cells during angiogenesis is impaired in the absence of filopodia [21]. Filopodium-like structures are also associated with migrating tumor cells during metastasis [22,23]. Robust invasiveness of breast and lung cancer cells in 3D-ECM is characterized by a special type of actin structure known as actin-spikes. These are short and dense F-actin filaments formed at the tip of the migrating cells. Unlike lamellipodia, formation of actin spikes is RhoA and formin FHOD3-dependent and Rac-independent [24,25].

Lobopodia-based migration

Distinct from the mesenchymal mode of migration, fibroblasts moving through a linearly elastic non-deformable cross-linked cell-derived matrix (stiffness 224–2454Pa) or fibronectin-coated synthetic 3D nanofibers form a cylindrical blunt end protrusion known as lobopodia [14,26]. Formation of lobopodia is integrin adhesion-dependent. However, in contrast with mesenchymal migration, lobopodial cells are not polarized, and Rac, Cdc-42, and PIP_3 signals are distributed uniformly throughout the cell. In these cells, the nucleus acts as a piston dividing the cell into a low-pressure rear and a high-pressure front compartment. Due to the high pressure, several blebs are formed at the lateral side of the lobopodia present at the leading edge. Actomyosin contractility at the front pulls the nucleus forward. The pulling force is transmitted through the intermediate filament vimentin, which is linked to the nuclear protein nesprin. The high pressure generated by the advancing nucleus leads to the formation of lobopodia [14,27]. Cytoplasmic streaming can also generate high-pressure lobopodia, as observed in *Amoeba proteus* [28]. Intriguingly, fibroblast sarcoma cells migrating through a cross-linked cell-derived matrix form lobopodia only in the absence of protease activity. Inhibition of MMPs switches the migration mode of polarized tumor cells from low pressure mesenchymal-based to high pressure unpolarized lobopodia-based migration, suggesting that the nuclear-piston might be an escape mechanism adopted by malignant cells to push the rigid and bulky nucleus through the dense matrix [29].

Amoeboid or bleb-based migration

In contrast with mesenchymal and lobopodial migration, the hallmark of amoeboid cell migration is its independence from cell-matrix adhesion. These cells are characterized by a rounded or irregular morphology, high actomyosin contractility, and higher motility rates compared with mesenchymal cells [30]. Leukocytes, which are classified as 'amoeboid' cells due to their rapid cell movement and frequent cell shape changes, migrate through 3D microenvironments in an integrin-independent manner both *in vitro* and *in vivo* [31]. In a non-degradable dense 3D microenvironment with small pore size, deformability of the nucleus becomes a limiting factor for effective migration. Neutrophils, having highly flexible nuclei, easily migrates through small gaps in the ECM [32]. There are several different modes of amoeboid cell migration [33]. Some amoeboid cells migrate using small round protrusions known as blebs. They are formed at leading edge of the cells due to increased intracellular pressure and detachment of the underlying cortex from the plasma membrane [34]. Blebbing amoeboid tumor cells, generated after protease-inhibition, rapidly squeeze through interstitial spaces in 3D matrices without the need for the matrix degradation machinery [35,36]. Unstable blebs are observed at the leading edge of migrating PGCs of *Zebrafish*; they are formed by cytoplasmic flow after the membrane-cortex connection ruptures in response to the chemokine SDF [37,38]. Stable blebs are formed by fibroblasts, several cancer cells and embryonic cells of *Zebrafish* when cultured under the conditions of high confinement and low adhesion [39–41], an *in vitro* model of 3D migration. Confined cells showed two different modes: small rounded A1 mode and a more elongated A2 mode with a rear uropod. A2 mode requires higher contractility and is

significantly faster than A1 mode. Cells can switch back and forth between the two modes. Interestingly, tumor cells and leukocytes show a preference for faster A2 mode which is also observed in *Dictyostelium discoideum* cells [42] and embryonic cells of *Zebrafish* [41]suggesting an evolutionary conserved mode of migration.

Swimming mode

Cells not only walk on solid substrates, 2D or 3D, they can also swim in solution. *Dictyostelium discoideum* amoebae show migration in 3Ds toward their chemotactic source, cAMP, when suspended in a chamber filled with Ficoll, a polysaccharide solution. Interestingly, the speed of migration in liquid is similar to that on a solid substratum. While migrating in liquid, amoebae rapidly change their shape, with transient lobes and spikes moving front to back. Akin to amoeboid movement, human neutrophils also show chemotaxis in suspension [43]. How do these cells move forward? Although several hypotheses had been proposed, this question remained unanswered until recently when a study by O'Neill and colleagues showed that macrophages swim by directional plasma membrane treadmilling. Localized activation of RhoA at the rear end causes actomyosin contractility and backward flow of membrane which is compensated by polarized vesicular trafficking from the rear end to front. Rearward surface treadmilling generates a viscous force tangentially at the cell-liquid interface that propels the cell forward. This rear end RhoA-mediated contractility is sufficient to drive motility without the presence of any protrusions such as lamellipodia or blebs at front [44]. Such a mechanism was first proposed, about 40 years ago, by the theoretical physicist Edward Purcell [45].

Biochemistry of NMII

NMII plays a central role in the generation of actomyosin contractility during cell migration. NMII has two main functions: first, it cross-links antiparallel actin filaments and second, it generates tension by pulling the actin filaments toward each other. Each NMII 'functional monomer' is a hexameric protein comprised of two heavy chains, two essential light chains (ELC), and two regulatory light chains (RLC). Each heavy chain is composed of a head domain, neck region, long helical coiled-coil rod domain, and a short non-helical tail. The highly conserved head domain contains the actin and ATP binding sites. The neck region binds the ELCs and RLCs. The essential light chain is required for stabilizing the head domain while phosphorylation of the RLC regulates NMII activity. The rod domain is required for the self-assembly of NMII into bipolar filaments. Unphosphorylated NMII forms a compact structure with head-to-tail interactions and a strong bond between the two head domains. This monomeric conformation prevents binding with actin filaments and hence is an inactive state. Phosphorylation of the RLC unfolds this compact conformation stimulating the assembly of bipolar NMII filaments via the extended rod domain and facilitates its interaction with antiparallel actin filaments (Figure 2A) [46]. Once assembled, the head domains hydrolyze ATP to move toward the barbed ends of the actin filaments resulting in sliding of antiparallel actin filaments in the opposite direction and contraction [47]. Recent studies, using structured illumination microscopy, have revealed in high resolution the organization of NMII filaments in fibroblast cells. Myosin bipolar filaments colocalize with the pointed-ends of actin filaments, alternating with α-actinin-rich regions that are enriched with the plus ends of actin. Additionally, NMII forms stacks oriented perpendicular to actin filaments, generating a 2D lattice (Figure 2B) [48–51].

Activity of NMII is regulated by serine and threonine phosphorylation of the RLC and heavy chain. Phosphorylation of the heavy chain mainly regulates NMII filament formation while phosphorylation of RLC plays an essential role in regulating both structure and activity of NMII. Heavy chain phosphorylation sites are on the coiled-coil domain and the non-helical tail region while RLC is phosphorylated at two distinct sites – Serine19 (Ser19) and Threonine 18 (Thr18). Phosphorylation at Ser19 transforms inactive NMII into an active state, promotes bipolar filament formation and ATP hydrolysis. The rate of ATP hydrolysis is further increased, in the presence of actin filaments, by an additional phosphorylation at Thr18 residue [47]. Interestingly, the two phosphorylation sites can have specific functions. Mono-phosphorylation at Ser19 is required for the maturation of focal adhesions distributed uniformly within the cell while di-phosphorylation of RLC, i.e. phosphorylation at both Ser19 and Thr18, spatially restricted to the rear end of the cell, promotes the formation of thick actomyosin bundles and large adhesion complexes [52]. Phosphorylation of the heavy chain and RLC is carried out by a multitude of kinases (reviewed in [47,53]). Some of these kinases activate NMII by directly phosphorylating the RLC as well as indirectly by inhibiting the myosin phosphatase (via its phosphorylation); other kinases buffer myosin activity by phosphorylating both activating and inhibitory sites.

NMII exists in multiple isoforms across Metazoa. Vertebrates have three main isoforms: NMIIA, NMIIB, and NMIIC, classified on the basis of different heavy chains. NMIIA and NMIIB are the most abundant isoforms found in mammalian cells. During initial assembly of the contractile system in a migrating cell, endogenous NMIIA and

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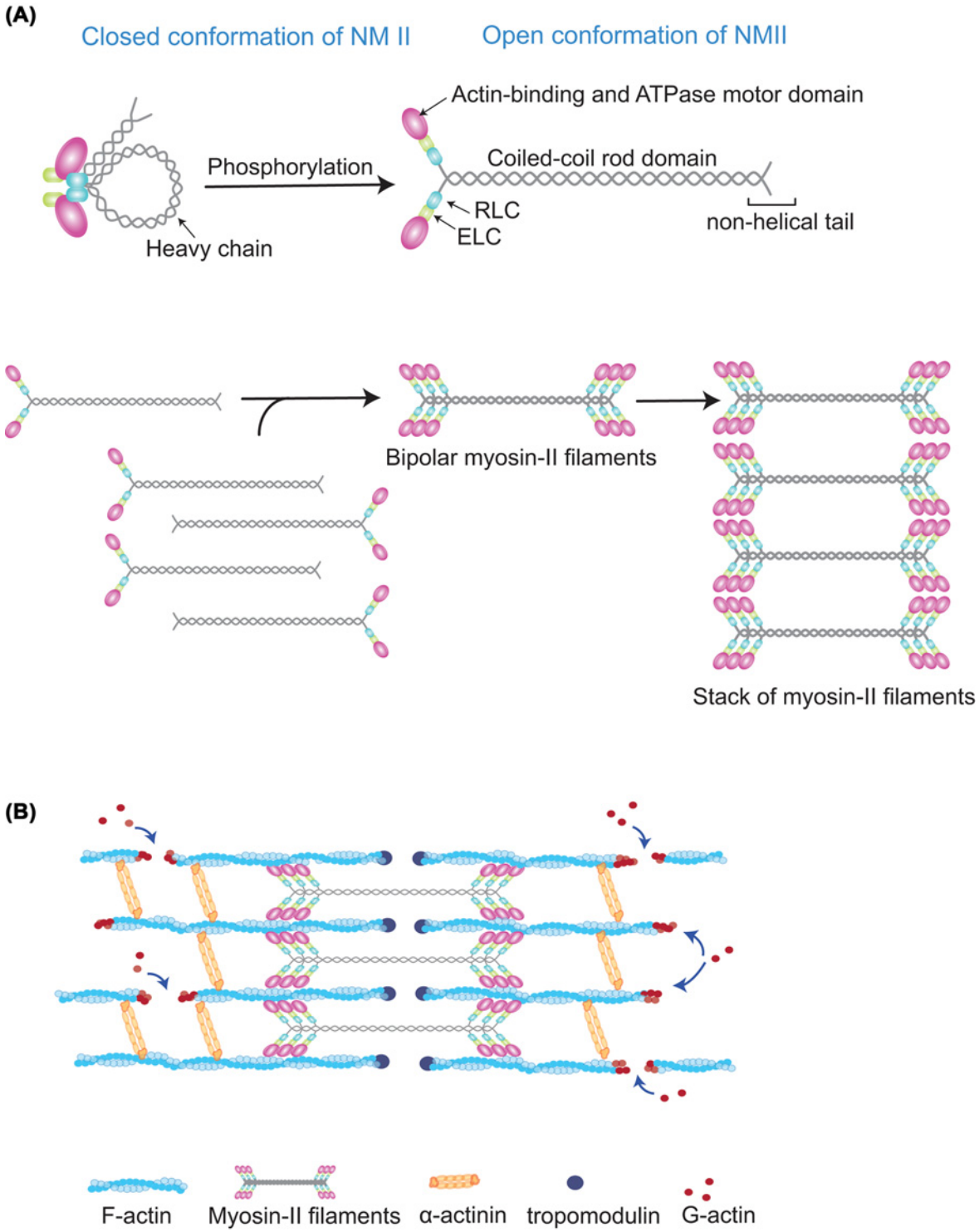

Figure 2. Structure and organization of NMII molecule

(**A**) NMII molecule consists of a head domain (pink) with an actin-binding and ATP-binding site, neck region includes essential light chain ELC (light green) and regulatory light chain RLC (dark green) and a long tail with a coiled-coil helical and non-helical region (grey). Phosphorylation of RLC transforms an inactive folded conformation of NMII molecule into an active extended form. Phosphorylated NMII monomers interact with each other via coiled-coil domain to form bipolar filaments. Bipolar NMII filaments assemble into stacks. (**B**) Sarcomeric-like organization of actin and NMII in the stress fibers and transverse arc. Barbed end with incorporating G-actin (red circles) overlap with α-actinin (orange) while the pointed end is enriched in tropomodulin (purple) and myosin-II filaments.

NMIIB isoforms coassemble to form heterotypic bipolar filaments [54–56]. The indistinguishable localization of the two isoforms changes with the maturation of stress fibers, when NMIIA is segregated to the nascent transverse stress fibers localized at the leading edge while NMIIB becomes enriched to more mature ventral stress fibers present at the center and rear end of the cell. This front to rear polarization is attributed to differential turnover rates of NMII isoforms, which ultimately results in self-sorting. NMIIA and NMIIB have equal efficiency to form bipolar filament, but the dissociation rate of NMIIA is higher than NMIIB. As a result, there is a gradual increase in the fraction of NMIIB that concentrate at the rear end of the cell due to retrograde flow [57–60]. Interestingly, the turnover rate of specific isoforms is governed by the C-terminal region of NMII [57]. Swapping the C-terminal domain of two different isoforms not only inverts their turnover rates but also reverses their distribution pattern [61]. Furthermore, NMII isoforms differ in two main kinetic properties: rate of ATP hydrolysis and duty ratio, defined by the time the myosin motor is bound to the actin filament for tension generation. NMIIA has the highest ATPase activity, sliding actin filaments much faster than NMIIB and NMIIC, while NMIIB has the maximal duty ratio [62,63]. Distinct subcellular localization and kinetic properties of the different isoforms indicate their unique functions [64].

Different spatio-temporal dynamics of myosin-II based contractility drive the different modes of 3D cell migration

Regardless of the mode of migration adopted under different 3D microenvironments, cells must exert a force upon their environment in one direction in order to propel themselves in the opposite direction. In all of the modes of 3D migration described above this force is generated by actin polymerization (reviewed in [10]) and myosin contractility. Forces generated by NMII-based contractility can be used to push or pull within the cell or by the cell on its environment. There is a mode of cell migration (osmotic engine-based motility) that is independent of actomyosin, and instead depends on polarized localization of water and ion channels to generate a flux of water through the cell [65], but we will not discuss it here.

Different spatial organizations of actin polymerization and myosin activity are associated with the different modes of 3D migration. Broadly speaking, they can be divided according to the localization of myosin at the front or back of the cell. Highly contractile phosphorylated NMII is enriched at the rear of the mesenchymal cells migrating toward a stiffer 3D matrix suggesting a role in directional migration [66,67]. Amoeboid breast tumor cells invading a 3D Matrigel have phosphorylated NMII present at their rear end. The force generated against the ECM by stress fibers and integrins at the rear pulls the matrix fibers toward the cell body, reorganizes, and aligns the matrix and promotes cell invasion (Figure 3A [i]) [68,69]. Within the cell, force generated by rear end contractility of amoeboid neutrophils or mesenchymal mammary gland carcinoma cells pushes the nucleus through the narrow pores of ECM (Figure 3A [ii]) [31,70], while anteriorly localized actomyosin fibers in adherent lobopodial cells pulls the nucleus like a piston, pressurizing the cytoplasm and push the cell forward (Figure 3B [i]) [27,29]. Also, high contractility at the leading edge of PGCs of *Zebrafish* facilitates bleb-based motility. Increased local NMII activity triggers separation of the cortex from the plasma membrane probably due to high intracellular pressure followed by cytoplasmic flow leading to the formation of blebs (Figure 3B [ii]). Cells treated with the NMII inhibitor, blebbistatin, lose their blebs, become more rounded and cease migration. Contrarily, cells expressing constitutively active MLCK have long-lived protrusions present throughout the cell periphery and they show abnormal migration behavior with lost directionality [37]. Finally, rearward flow of the actomyosin cortex plays an essential role in cell motility when cells are suspended in liquid (swimming mode) or placed under high confinement and low adhesion (stable-bleb based motility). Frictional forces generated by the retrograde cortical flow at the cell-liquid or cell-substratum interface produce sufficient traction for forward cell movement (Figure 3C) [39–41,44].

Role of actomyosin contractility in plasticity of cell migration

Intriguingly, cells can readily switch from one migration mode to another in response to varying intrinsic and extrinsic factors [13,71]. Such plasticity has been observed in pathological as well as physiological contexts. When treated with MMP inhibitors, tumor cells transform from mesenchymal to amoeboid mode, squeezing through narrow spaces in the 3D matrix without the need for ECM degradation. Thus, tumor cells compensate for the loss of one specific mode by adopting a different strategy for migration [9,29,35]. Also, plasticity of migration mode plays a crucial role during embryogenesis and wound healing when cells encounter diverse environmental conditions while infiltrating different tissues [41,72].

Actomyosin contractility is one of the key factors that favors transition into a different mode of cell migration. Many cell types, normal or tumorous, including epithelial, mesenchymal, muscle, and immune cells cultured under high confinement and low adhesion conditions rapidly switch into fast A2 amoeboid mode of migration [39,40]. This

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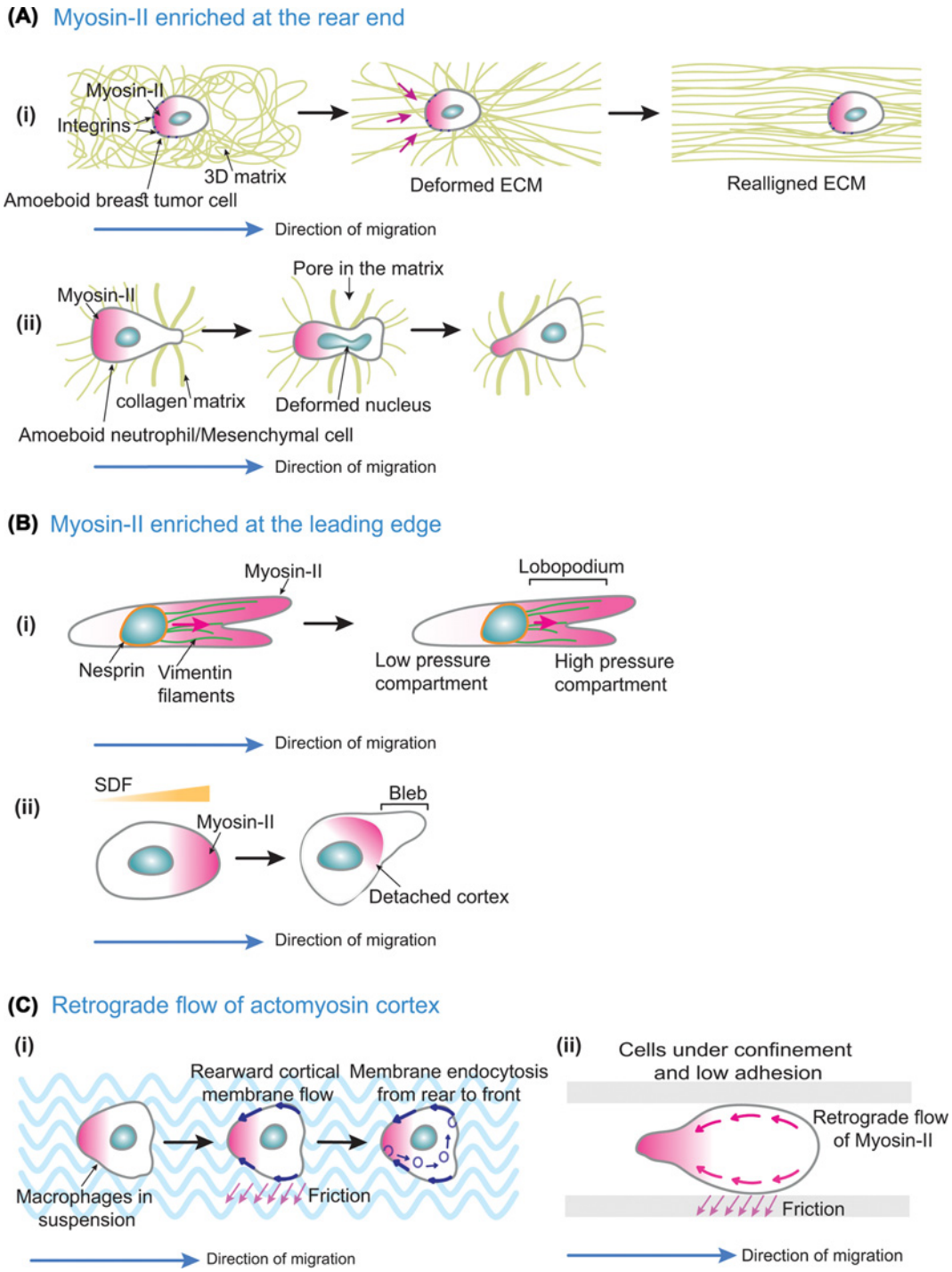

Figure 3. Spatio-temporal dynamics of myosin-II contractility during different modes of 3D cell migration

(**A**) **(i)** Rear end contractility generates traction force through integrins and stress fibers. This force pulls the matrix toward the cell body and realigns ECM that allow smooth migration of the cells. **(ii)** Myosin-II contractility at the rear end facilitates translocation of nucleus through restricted gaps in the matrix. (**B**) **(i)** In lobopodial cells, actomyosin contractility at the leading edge pulls the nucleus via intermediate filament, vimentin (green) linked to nesprin, a nucleoskeleton protein (orange). Pulling force generates high intracellular pressure at front pushing forward the leading edge. **(ii)** Increased local myosin-II activity at the leading edge (due to high concentration of a chemokine, SDF) of amoeboid cells weakens membrane-cortex attachment forming blebs, which helps the cells to squeeze through the dense matrix. (**C**) Retrograde flow of actomyosin cortex in the swimming macrophages **(i)** or in the cells cultured in confined and low adhesion 3D microenvironment **(ii)** generates a non-specific friction which propels the cells forward.

transition was found to depend on high levels of cell contractility. Increasing contractility by genetic or pharmacological perturbations increased the percentage of cells switching to fast amoeboid mode while inhibiting NMII activity reduced the number of amoeboid cells drastically [39]. The mechanism by which high confinement and low adhesion favors high cell contractility is currently unknown. Likewise, application of a serum phospholipid lysophosphatidic acid up-regulates cortical myosin II in isolated embryonic cells of *Zebrafish* driving a switch from mesenchymal or unstable blebbing mode to a polarized stable bleb state of migration. Not only *in vitro*, progenitor cells in the gastrulating *Zebrafish* embryo expressing constitutively active RhoA readily transform into stable-bleb based motility. Similar transformations are often observed in local areas of high contractility, such as wound sites [41]. Increased actomyosin contractility is also required for switching between two different adhesion-dependent modes of cell migration – 'low pressure' lamellipodial to 'high-pressure' lobopodial mode. Decreasing NMII activity switches back the cells to lamellipodial-based migration [27,29]. Actomyosin contractility-mediated traction force is responsible for the stretch and recoil of the matrix. Reducing contractility switches the cells undergoing sling shot migration to continuous mesenchymal mode of migration [15]. Thus, high contractility appears to be a universal switch transforming mesenchymal cells into different migration modes under diverse 3D environment.

Conclusion and outstanding questions

Accumulating evidence suggests that an individual cell can display multiple migration behaviors. In response to varying local 3D matrix conditions or signals, the intracellular cytoskeletal elements can reorganize, switching to a more efficient mode of migration. These studies raise several questions such as: how do the extracellular cues communicate with the intracellular machinery (actomyosin contractility) to drive various modes of migration? How are the spatio-temporal dynamics of NMII contractility regulated during different modes? As discussed above, myosin contractility is a key factor for the switch of motility mode in varying conditions. How does contractility drive the switch to different modes of motility?

Most of the modes of migration described so far have been identified in *vitro* under varying controlled environmental conditions. Therefore, an outstanding question to be addressed in future studies is when and where these different modes of migration are employed in animals. *In vitro* 3D models used for studying cell migration do not recapitulate the complexity of *in vivo* conditions. Hence, high spatio-temporal resolution imaging *in vivo* at the subcellular level is needed for understanding 3D cell migration occurring during biological processes such as tissue morphogenesis, repair, and regeneration, as well as cancer metastasis. Furthermore, insight into the precise mechanisms of motility utilized by normal versus tumorous cells in 3D microenvironment might help in designing and developing new strategies that inhibit cancerous cell migration without affecting healthy cells.

Summary

- Normal as well as transformed cells show diverse migration behaviors in different 3D microenvironments. Different modes of 3D migration are largely classified on the basis of their morphology, dependence on cell-matrix adhesion, and actomyosin contractility.
- Spatio-temporal activity of myosin-II defines the mechanism of motility in different modes. Rear localization of myosin is a hallmark of mesenchymal migration, whereas localization of myosin in amoeboid migration can be either frontal or rear-end enriched.
- Increased myosin II contractility is commonly responsible for plasticity of migration in various 3D microenvironments.

Competing Interests

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

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Author Contribution

P.A. and R.Z.B. developed the concept and outline. P.A. wrote the first draft and provided figures. R.Z.B. and P.A. both edited and revised the text.

Abbreviations

ECM, extracellular matrix; LPA, lysophosphatidic acid; MMP, matrix metalloprotease; PGC, primordial germ cell; RLC, regulatory light chain; NMII, non-muscle myosin-II.

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