Rear actomyosin contractility-driven directional cell migration in three-dimensional matrices: a mechano-chemical coupling mechanism

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Cell migration is of vital importance in many biological processes, including organismal development, immune response and development of vascular diseases. For instance, migration of vascular smooth muscle cells from the media to intima is an essential part of the development of atherosclerosis and restenosis after stent deployment. While it is well characterized that cells use actin polymerization at the leading edge to propel themselves to move on two-dimensional substrates, the migration modes of cells in three-dimensional matrices relevant to in vivo environments remain unclear. Intracellular tension, which is created by myosin II activity, fulfils a vital role in regulating cell migration. We note that there is compelling evidence from theoretical and experimental work that myosin II accumulates at the cell rear, either isoform-dependent or -independent, leading to three-dimensional migration modes driven by posterior myosin II tension. The scenario is not limited to amoeboid migration, and it is also seen in mesenchymal migration in which a two-dimensional-like migration mode based on front protrusions is often expected, suggesting that there may exist universal underlying mechanisms. In this review, we aim to shed some light on how anisotropic myosin II localization induces cell motility in three-dimensional environments from a biomechanical view. We demonstrate an interesting mechanism where an interplay between mechanical myosin II localization and biochemical myosin II activation triggers directional migration in three-dimensional matrices. In the case of amoeboid three-dimensional migration, myosin II first accumulates at the cell rear to induce a slight polarization displayed as a uropod-like structure under the action of a tension-dependent mechanism. Subsequent biochemical signalling pathways initiate actomyosin contractility, producing traction forces on the adhesion system or creating prominent motile forces through blebbing activity, to drive cells to move. In mesenchymal three-dimensional migration, cells can also take advantage of the elastic properties of three-dimensional matrices to move. A minor myosin isoform, myosin IIB, is retained by relatively stiff three-dimensional matrices at the posterior side, then activated by signalling cascades, facilitating prominent cell polarization by establishing front–back polarity and creating cell rear. Myosin IIB initiates cell polarization and coordinates with the major isoform myosin IIA-assembled stress fibres, to power the directional migration of cells in the three-dimensional matrix.

1. Introduction

Cell migration is of vital importance in many biological processes, including organismal development, immune response and development of vascular
Cell migration is a highly orchestrated multi-step process. (a) Driven by polymerization of actin filaments, cells that migrate first become polarized and extend protrusive structures; (b) weak nascent adhesions are formed under the lamellipodium owing to the binding of integrins to the extracellular matrix; (c) the nucleus and cell body are moved forward by the tension created by stress fibres; and (d) the cell retracts its trailing edge by destabilizing and releasing focal adhesions of this region. (e) Integrins are linked to the actin cytoskeleton through multiple focal adhesion molecules, including kinases like FAK, and actin-binding proteins such as talin, vinculin, paxillin and α-actinin. (Online version in colour.)
broad front protrusion-driven migration mode seen in two-dimensional cases. The migration mechanism in the three-dimensional environment remains unclear. Cells migrating in three-dimensional matrices adopt either a mesenchymal or amoeboid mode [35]. In mesenchymal migration, which bears some resemblance to lamellipodia-driven two-dimensional migration, cells adopt elongated morphology and use percellular matrix proteolysis to extend front actin filaments-based protrusions to move themselves directionally ahead in an adhesion-dependent manner [36–38]. In amoeboid mode typically seen in invasive tumour cells, leucocytes [39] and fibroblasts [34], cells exhibit rounded morphologies and use different strategies, contraction-based membrane blebbing together with myosin II-enriched cell rear, to migrate [35,40–43]. Matrix degradation by protease is not needed in the movement. It has been suggested that mesenchymal and amoeboid migration are powered by actin polymerization and actomyosin contraction, respectively [42,44].

Various biomimetic three-dimensional matrices within which cells embed include gels based on native matrix components (Matrigel, fibril, collagen, etc.), synthetic materials (poly(ethylene glycol) and biological constructs (dermal explants). These materials assemble into various fibre structures differing in mechanical properties, such as stiffness, fibre diameter and pore size. Experimental investigations suggest that cells migrating in three-dimensional Matrigel or collagen gels displayed characteristic amoeboid modes and myosin II was recruited towards the cell rear under the action of a tension-dependent mechanism. A recent study by Petrie et al [34] suggested that modes of three-dimensional migration were modulated by an association of actomyosin contractility and mechanical properties of the matrix. They found RhoA mediated high actomyosin tension together with linear elasticity of dermal explants or cell-derived matrix switched cells to a migration mode characterized by front blunt, cylindrical protrusions, e.g. lobopodia. Lobopodia-based migration did not require the canonical polarization of PI3, Rac1 and Cdc42 activity typically seen in two-dimensional migration and was independent of lamellipodia formation. The migration mode was determined intrinsically by myosin II activity, consistent with previous actomyosin contractility-based three-dimensional migration modes [35,39]. However, the localization of myosin II remains to be elaborated.

Cells exhibit ‘wisdom’ to regulate their behaviour in response to external perturbations [45]. Cells of the same type use different modes to migrate depending on the elastic properties of the matrix and biochemical signalling factors [46,47]. It has been suggested that cell migration should be considered as continuous modes balanced among adhesion, contractility and mechanical properties of the matrix, rather than strictly separate mechanisms [40]. We note that there is compelling evidence from recent theoretical and experimental work that myosin II accumulates at the cell rear, either isoform-dependent or -independent, leading to directional three-dimensional migration driven by posterior myosin II contractility. The scenario is not limited to amoeboid migration, and it is also seen in mesenchymal migration in which lamellipodia-based motility is often expected, suggesting there may exist universal underlying mechanisms. In this review, we aim to shed some light on how anisotropic myosin II localization induces cell motility in three-dimensional environments from a biomechanical view. We demonstrate an interesting mechanism where the interplay between mechanical myosin II recruitment and biochemical myosin II activation triggers directional migration in the three-dimensional matrix.

2. Isoforms, structures and functions of myosin II

Actomyosin tension created by myosin II activity, one of the foremost sources of intracellular forces, plays a pivotal role in several fundamental cellular processes, including cell migration, division and morphogenesis [12,48–51]. Myosin II molecules can move towards the plus (barbed) end of actin filaments via the hydrolysis of adenosine triphosphate at the myosin head, propelling sliding between them and creating tension [13,50]. This well-established paradigm of tension creating by actomyosin (the protein complex composed of actin and myosin), termed cross-bridge cycling, is recognized as the fundamental contractile apparatus in almost all forms of muscle cells and non-muscle cells [50].

In addition to smooth muscle, cardiac and skeletal myosin II, there are three isoforms of non-muscle myosin II: myosin IIA (MIIA), myosin IIB (MIIB) and myosin IIC (MIIC). Both MIIA and MIIB are typically seen in most mammalian cells [12,13]. They fulfill different but overlapping functions in cell migration. MIIA is situated all through the cell, even in protrusions, but not including the leading edge. It plays a crucial role in retracting cell edges and adhesion maturation at the leading edge [26,52]. MIIB localizes in the central and rear regions, but not in protrusions [53]. It helps to determine the overall morphology of the cell as well as facilitate adhesion maturation as evident from experimental observations that cells with inhibited MIIB activity exhibit small adhesions, round morphology and extend multiple protrusions [26,54]. The release of adenosine diphosphate from MIIB is rather slow owing to its high affinity for adenosine diphosphate when compared with other myosin isoforms [55], making MIIB well suited for creating tension for longer duration and less energy cost than MIIA [13]. This may be an indication of MIIB’s role in prolonged cell migration in chronic diseases like atherosclerosis. The intracellular localization of both isoforms depends on the self-assembly regions in the coiled-coil C terminus [13,56]. The function of MIIC remains to be explored. Unlike the other two non-muscle isoforms, this isoform is not expressed in fetal tissues [57].

A myosin II molecule is constituted of three parts: two myosin heavy chains (MHCs) of 230 kDa which are composed of head and tail domains with the latter appearing as a coiled-coil morphology, holding the two heavy chains together, containing four myosin light chains (MLCs); two 20 kDa regulatory light chains (RLCs), which bind the heavy chains in the neck region; and two 17 kDa essential light chains (ELCs), which function to stabilize the heavy chain structure. A representation of the myosin II structure is shown in figure 2. Previous studies have determined a relatively clear cloud of signalling cascades in regulating actomyosin activity. The actomyosin contraction system is regulated in at least two independent pathways, a Ca$^{2+}$-dependent pathway and a Rho-dependent pathway that does not depend on Ca$^{2+}$ [4,41,58]. The former leads to MLC kinase (MLCK) activation and subsequent MLC phosphorylation and the latter takes effect either by direct MLC phosphorylation or by blocking MLC phosphatase (MLCP) phosphorylation. Moreover, myosin II can also be regulated...
by other regulatory proteins like S100A4 and inhibitory phosphorylation at the heavy chains [12]. The signalling pathways by which myosin II activity is regulated are shown in figure 3.

3. Tension-dependent myosin II recruitment towards the cell rear

Myosin II functions as the most prominent intracellular tension contributor of actomyosin structures through biochemical signalling [12]. Recently, this well-recognized cloud has been enriched by recent findings that mechanical tension can feed back to regulate myosin II binding to actin filaments. Accumulated data suggest that myosin II motors prefer to bind to stretched actin filaments bearing large tension. Experimental examinations performed by Fernandez-Gonzalez et al. [59] showed that myosin II preferred to stabilize at the regions of the cortex in Drosophila cells bearing increased tension, and conversely relieving tension resulted in a rapid loss of the cortex in Drosophila. Examinations performed by Fernandez-Gonzalez et al. [59] indicated that myosin II motor domain (S1) probes preferred to locate in the posterior portion and cleavage furrows of fixed fibroblasts, with actin filaments bearing more tension owing to the interactions with myosin II. Similar myosin II enrichment in the cortex can also be observed by applying external stretching forces to the portion using a microcapillary [61]. This may account for the affinity of myosin II filaments assembly to lamellipodia bundles and lateral concave arcs of cells, leading to increased myosin II accumulation and greater tension in these structures through subsequent biochemical activity [29].

Several studies suggest that this tension-dependent myosin recruitment is aroused by the correlated change in MLC phosphorylation. However, this hypothesis is inconsistent with the results that the level of MLC phosphorylation does not change [29,62,63] or even increases [64,65] in the presence of blebbistatin, which is an effective myosin II inhibitor. Previous experimental results also suggest that blebbistatin inhibited myosin II activity by inducing a swelling conformation in S1 instead of the classical MLC signalling cascades [66]. A more reasonable explanation has been given by Uyeda et al. [61]. They suggest that this tension-dependent myosin recruitment depends on mechanical cues rather than the signalling proteins. They demonstrate that, in the experiment, neither cortexillin I nor PTEN, two signalling proteins which have been reported in the recruitment of myosin II to stretched cortex [60,67], nor MLC phosphorylation participates in the process. The underlying mechanical mechanism given by them is: stretching causes the untwisting of the filament helix (demonstrated recently by molecular dynamics simulations [68]) and binding of skeletal S1 to actin filaments could slightly untwist the helix of the latter [69], making it plausible that S1 prefers to bind to stretched actin filaments. This explanation is supported in the theoretical work by Luo et al. [49]. Assuming that the binding of myosin II induces changes in twisting degree of the helix in actin filaments in Monte Carlo simulations, they capture the experimental observations of tension-dependent myosin II accumulation.

Mechanosensory focal adhesion components, such as talin, vinculin and α-actinin, are also expected to play a role in the tension-dependent myosin II recruitment. Cells orchestrate these adhesion molecules precisely to fulfill mechanotransduction events. It has been well established that integrins initially link to actin cytoskeleton through talin, which bears actomyosin tension aiding the formation of nascent focal adhesions [70,71]. Previous results found that stretching talin exposes new sites for vinculin binding, and this would support the idea that myosin II prefers to bind stretched actin filaments [72]. The scenario is enriched by a most recent work suggesting that α-actinin competes with talin to bind cytoplasmic domain of β3 integrins [73]. It was suggested that talin initially binds to β3 integrins and triggers the formation of nascent adhesions, then α-actinin replaces talin when these focal adhesions are mature.

The tension-dependent myosin II accumulation is supported by the latest findings by Iwadate et al. [74]. They found Dicyostelium cells accumulated myosin II, assembled into force-responding filamentous structures, at both stretching boundaries. Accumulated myosin II filaments induced directional migration of the cells, in which biochemical
signalling-initiated actomyosin contraction was needed. The mechanism would enable cells to escape from external mechanical stimuli owing to enhanced contractility in the locally stretched portion of the cell cortex. Fragments of a fish keratocyte that contain the actomyosin machinery but lack essential cell components provide a remarkable platform to test this. When a discoid stationary fragment of a fish keratocyte was pushed by the tip of a microneedle, the stimulated fragment started to move unidirectionally away [75]. This may be owing to the stretch of the cell cortex enhancing the contractility at the site of deformation by the recruitment of myosin II filaments [61].

4. Myosin II’s back accumulation commits cells into a polarized, moving state

The tension-dependent recruitment of myosin II makes a significant contribution to the molecules’ initial asymmetric accumulation in cells ready to move. Actin filaments at the leading and trailing edges of cells ready to move exhibit a difference in contact with membrane (front) or intracellular portion of focal adhesions (rear)—pushing versus pulling. Thus actin filaments at the posterior of the cells are more stretched than those at the opposite edge. Owing to myosin II’s affinity to stretched actin filaments, myosin II resides preferentially at the rear of migrating cells, creating a slight anisotropic distribution of tension. This aligns well with the experimental observations that pre-existing polarization cues induce steady-state cortical flow and destabilize the cortex [76,77]. Anisotropic myosin II distribution is essential in establishing cell polarization, which is considered as a prerequisite of cell movement [40]. Various migration modes differ by the degree of polarization. In general, mesenchymal three-dimensional migration adopts a severe polarization with apparent cell front and rear, while amoeboid three-dimensional migration displays just slight polarization with uropod-like structure.

Cell polarity (referring to the front–back polarity in cell migration), the ability of a cell to form a vectorial axis [78], is crucial to directional cell migration. Almost all migrating cells exhibit a certain degree of cell polarity, which assists in initiating cell movement. Cells need to polarize themselves to commit to a moving state [2,40,75]. MIIB’s accumulation at the cell rear is essential for polarization by creating a distinct rear [53]. Experimental investigations show that myosin II null mutant Dictyostelium cells cannot be polarized in shape on sticky substrates, although the cells extend pseudopod protrusions at the front side [6]. Myosin II exhibits an asymmetric accumulation in moving cells. It has been observed in experiments that myosin II resides preferentially at the rear of migrating cells in contrast to the uniform distribution of myosin II in stationary cells [75,79,80]. Local application of calyculin A at one side of migrating keratocytes makes this side become a rear rich in myosin II, increasing the frequency of motility initiation [81]. Myosin II activation via MLC phosphorylation results in the formation of an extended rear and increased directional migration in fibroblasts [53].

A recent mesoscopic mean-field simulation (a simulation method based on mean-field theory on scales in the range of nano- to micrometres) of models constituted of filaments, motors and cell boundaries provides a direct validation of myosin distribution in static and moving cells [82]. The results demonstrate that, in the static state, myosin II distribution is rather isotropic throughout the cell, and the distribution of actin filaments is rotationally symmetric and relatively flat. However, in the moving state, both myosin II and actin filaments are distributed with a peak density at the back of the cells, in comparison with a vanishingly small density of myosin II and flat distribution of actin filaments at the front. Myosin II accumulation at the back of the cells essentially directs the cells to commit to a polarized, moving state, which is in accordance with the suggestion in Hawkins et al. [83] that myosin II transport first induces cortical instability and then leads to motility in a three-dimensional environment. In the absence of myosin II, the cells are driven into a symmetric, static state. The calculation results obtained by Du et al. [82] clearly show that if the initial myosin II distribution is not exactly isotropic the resulting tension anisotropy applies asymmetric force on the boundary, destabilizing the static state and giving rise to the locomotion of the cell.

5. Tension-dependent myosin II accumulation plays a role in amoeboid three-dimensional migration

Cells in vivo often move in a three-dimensional environment, like an extracellular matrix or a tissue of cells. Cell polarization is often visible in migrating cells and is considered as a prerequisite in cell migration, as it determines the moving direction [40]. However, tumour cells exhibit a round morphology and membrane blebs with a slight polarization—uropod at the rear, instead of significant polarization in shape—an apparent front or back. Recent investigations have confirmed the uropod, which is enriched in myosin II and exhibit high actomyosin tension, plays a crucial role in amoeboid cancer migration in three-dimensional matrices. Round amoeboid migration of cancer cells takes at least three distinct rear myosin II activity-driven modes distinguished by bleb features: rear, multiple and large hemispherical blebs [40,43,46]. Note that these modes are distinct from previously established amoeboid migration mode on two-dimensional substrates, which shares some features with two-dimensional mesenchymal migration. In the mode, front protrusions determine the moving direction and posterior myosin II activity detaches the cell rear [44,84–86].

A recent experiment found that MDA-MB-231 human breast cancer cells migrated in three-dimensional Matrigel with a rounded morphology and with myosin II accumulating at the cell rear, while the cells display neither lamellipodia nor bleb extensions at the front side [43]. Silencing Arp2/3, the main actin polymerization nucleator in lamellipodia, did not affect the velocity of migration. Whereas, inhibiting myosin II activity almost completely abolished cell movement. Accumulation of phosphorylated MLCs and intensive blebbing activity were observed at the cell rear, indicating actomyosin tension at the site. Strong actomyosin tension in the uropod generated traction forces on adhesions at the side and rear to power the cells to migrate. It was suggested that the rear blebbing activity was caused by the strong actomyosin tension at the site and did not contribute to cell movement. Another investigation reported A375 melanoma cells migrating through three-dimensional Matrigel and collagen exhibited similar rounded shape with many membrane blebs and uropod rich in errin, myosin II and other proteins [40]. The migration of
the cells was also driven by rear actomyosin tension bearing a resemblance to amoeboid migration of MDA-MB-231 cells, but the details differ. In brief, actomyosin tension created by rear myosin II activity endowed the cells with traction forces through bleb activity and directly determined the migration direction. Myosin II accumulated and was then activated by MLC phosphorylation at the cell rear, creating high actomyosin tension at the cell boundaries. Thus, hydrostatic pressure was exhibited on the cytoplasm, releasing many membrane blebs through the membrane except the rear uropod. Each bleb generated a small force, creating a net force to drive the cells to migrate towards the side opposite to the uropod.

Considering that the blebs represent merely a result from cortical tension concentrating in the rear region [40,43,87], the mechanism behind the appearance of rear blebs in MDA-MB-231 cell migration and many blebs in A375 cells is also similar to the third round amoeboid migration mode featured by a large, hemispherical bleb [42,88,89]. In that case, high actomyosin tension is maintained through the actin cortex mostly owing to increasing myosin II activity at the cell rear, creating hydrostatic pressure to form growing blebs towards the opposite side of the rear [40]. In essence, migration represented by large blebs is powered by the rear myosin II activity rather than the front bleb.

Tension-dependent recruitment of myosin II is expected to make a significant contribution to its asymmetric accumulation in migrating cells. Actin cytoskeleton in anterior and posterior regions exhibits a difference in contact with membrane—pushing versus pulling—thus actin filaments at the posterior of the cells are more stretched than those at the opposite side. Owing to myosin II’s affinity to stretched actin filaments, myosin II resides preferentially at the rear of migrating cells, creating an anisotropic distribution of tension. The expected tension-dependent mechanism in cell migration is illustrated in figure 4. This aligns well with the experimental observations that pre-existing polarization cues induce steady-state cortical flow and destabilize the cortex [76,77]. Note that the mechanism would be most effective to accumulate myosin II at the rear for cells in three-dimensional environments. Actin filaments at the posterior of cells embedded in three-dimensional matrices would be stretched along a wide curved surface along the rear membrane, in comparison with a narrow flat surface along the rear substrate in two-dimensional cases. Thus, actin filaments in contact with the rear membrane are stretched in a much wider space through adhesion system than that in the two-dimensional scenario. The front side of the cell is strongly pushed against by the surrounding matrix. Even in the case of low-adhesion three-dimensional amoeboid migration, myosin II still prefers to localize at the free rear rather than the strongly pushed opposite side. Thus, myosin II will be effectively recruited towards the cell rear, helping to increase the degree of polarization.

6. Isoform-dependent myosin II accumulation induces directional migration in three-dimensional matrices

6.1. Matrix stiffness affects three-dimensional migration

Matrix stiffness is a rather effective effector for cell behaviour and correlates with many physiological and pathological processes. It has been well established that cells sense the substrate stiffness by polarizing stress fibres and in doing so create strong cytoskeletal tension to propel the cell to move. Cells would readily polarize and migrate when cultured on a stiff matrix [90]. Native matrix is characterized by its intrinsic three-dimensional structure and low stiffness, which both affect cell migration significantly. Investigators have reported that the elastic properties of the matrix dictate the migration mode of cells in three-dimensional matrices [34]. It should be noted that the cytoskeletal polarization and migration fashion of cells on soft substrates and in three-dimensional matrices is distinct from the scenario typically seen on stiff two-dimensional substrates [91]. Polarization of stress fibres in soft two- or three-dimensional systems is always independent of the moving direction, leading to random migration without an obvious orientation [92,93]. Whereas cells cultured on a stiff two-dimensional substrate polarize stress fibres in the moving direction, exhibiting directional migration [91]. A matrix with stiffness gradient is needed to achieve directional migration, durotaxis, in a soft matrix system [93,94].

Cells often need to migrate directionally to fulfill physiological processes in response to directional cues, such as soluble molecules (chemotaxis), adhesion proteins (haptotaxis) and stiffness (durotaxis) [95]. Among these forms of directional migration, chemotaxis may be the most well understood and is most commonly seen in in vitro experiments, while haptotaxis and durotaxis are much less understood [65]. Durotaxis, the tendency of cells to migrate from soft to rigid matrix in the absence of any soluble biochemical stimuli, has been demonstrated in a large number
of experimental observations [94,96–98]. Durotaxis seems to provide an excellent mechanical fashion for cells to move through the three-dimensional matrix in which they are trapped. It has been suggested that soft three-dimensional matrix microenvironment affects cell migration by the gradient in matrix stiffness [93]. Cells are able to migrate directionally if persistent spontaneous polarization is maintained, even if no external cues exist [99]. As we discussed in the previous sections, this can be fulfilled by inducing spontaneous polarization through accumulating myosin II at the cell rear, even if front protrusions are not so prominent as on two-dimensional surfaces.

6.2. Myosin IIIB accumulation at the cell rear induces directional migration in three-dimensional matrices

In some cases like mesenchymal three-dimensional migration, cells take elongated morphology, and actin filaments are stretched at the cell rear within a narrow space. Tension-dependent mechanism plays a minor role in these cases while only a limited fraction of myosin II is recruited at the cell rear by the mechanism. This time myosin II exhibits isoform-dependent accumulation at the cell rear owing to the affection of self-assembly regions of the coiled-coil C terminus [13,56]. The elastic properties of the matrix have a significant impact on the migration mode in three-dimensional matrices. Experimental observations showed that as mesenchymal stem cells (MSCs) were deposited within three-dimensional matrices with stiffness gradient, the cells also exhibited durotaxis as seen in two-dimensional durotaxis [93]. The cells also migrated directionally in relatively stiff matrices, whereas this decayed to random migration [93]. MIIB only accumulates at the cell rear in relatively stiff three-dimensional matrices, yet is uniformly distributed within the cell body in soft three-dimensional matrices. It is most intriguing to note that anisotropic distribution of MIIB is promoted as matrix stiffness increases, in contrast with a slight anisotropic yet constant distribution of MIIA [93].

MSCs in three-dimensional matrices exhibit multiple lateral lamellipodia [93], which is indicative of random migration and a minor role of front protrusions in migration [2]. However, these cells still exhibit directional migration in a three-dimensional matrix, including stiff matrix and stiffness gradient cases [93]. Cells can move directionally to fulfill physiological roles even in a very soft three-dimensional matrix provided gradient stiffness exists in the matrix. It was suggested that the accumulation of minor isoform MIIB at the cell rear drives the cells to move directionally in three-dimensional matrices, including cases of stiff matrices and durotaxis [93]. Previous investigations have confirmed that MIIB functions to establish front–back polarity [26] and create cell rear [53]. MLC phosphorylation activates the accumulated MIIB, inducing prominent actomyosin tension at the cell rear, producing large, stable adhesions and defining the morphology of the rear [53]. Although showing no apparent accumulation at any side in three-dimensional matrices with variable stiffness, MIA is also essential in cell migration by initiating the formation of stress fibres to which MIIB then binds and stabilizes [26]. Coordination between MIA and MIIB is needed in directional three-dimensional migration.

Tension-dependent mechanism can make a contribution, at least a minor one, to the accumulation of both myosin II isoforms at the cell rear, although it seems difficult to distinguish the effect contributed by the tension-dependent mechanism from that contributed by structural features in the C terminus for MIIB accumulation at the cell rear. It has been observed that MIIA in MSCs in three-dimensional matrices exhibits a slight, persistent accumulation at the cell rear in the whole studied stiffness range [93]. Considering the MIIA back accumulation is stiffness-independent and is not intrinsically located there, it is the tension-dependent mechanism that may drive the slight MIIB accumulation.

7. Summary

It is said that cells have ‘wisdom’ to regulate their behaviour in response to external perturbations [45]. In the context of the three-dimensional environment, cells exhibit such wisdom to migrate and in doing so fulfil physiological and pathological
roles. They use rear contraction apparatus to propel themselves ahead when the front protrusions typically seen on a two-dimensional surface are lacking. There is compelling evidence from theoretical and experimental work that myosin II accumulates at the cell rear, in either an isoform-dependent or a general way, leading to distinct three-dimensional migration modes dominated by myosin II contractility. As far as we are concerned, not much is known about the mechanism underlying these migration modes. Biomechanical factors, including a tension-dependent myosin II recruitment, the elastic properties of matrices and the instability and polarization of cells caused by anisotropic myosin II distribution, are expected to be key players in the process. In this paper, we attempt to decipher these migration modes from a biomechanical viewpoint by summarizing a large body of mathematical modelling and experimental work. Myosin II can be recruited at the cell rear under the action of a tension-dependent mechanism. Subsequent biochemical signalling pathways initiate actomyosin contractility, producing traction forces on the adhesion system or creating prominent motile forces through blebbing activity, to drive cells to move directionally. The full scenario is depicted in figure 5. This mechanism is most effective in amoeboid three-dimensional migration of tumour cells. These cells exhibit a rounded shape, with slight polarization displayed as a uropod-like structure. Abundant myosin II accumulates at the cell rear owing to actin filaments at the portion being stretched in a wide space in contact with the matrix through adhesions. Thus strong actomyosin tension is created by subsequent MLC phosphorylation to propel the cells to move towards the side opposite to the uropod. In mesenchymal three-dimensional migration, cells take an elongated morphology, only a limited fraction of myosin II is recruited at the cell rear and the tension-dependent mechanism plays a minor role. This time cells take advantage of the elastic properties of the three-dimensional matrix to recruit a certain minor isoform, MIIIB, at the cell rear. MIIIB activity induces prominent cell polarization by establishing front–back polarity and creating cell rear. This works in coordination with the polarization of MIIA-assembled stress fibres to direct the cells to commit to a polarized, moving state.

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References


73. Roca-Cusachs P, del Rio A, Puklin-Faucher E,

74. Iwadate Y, Okimura C, Sato K, Nakashima Y, Tsujioka

75. Verkhovsky AB, Svitkina TM, Borisy GG. 1999 Self-


77. Mayer M, Depken M, Bois JS, Juelicher F, Grill SW.


