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Boris Rubinstein & Inês Mendes Pinto

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Epithelia migration: A spatiotemporal interplay between contraction and adhesion

Boris Rubinstein¹ and Inês Mendes Pinto^{2,*}

¹Stowers Institute for Medical Research; Kansas City, KS USA; ²International Iberian Nanotechnology Laboratory; Braga, Portugal

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Epithelial tissues represent 60% of the cells that form the human body and where more than 90% of all cancers derived. Epithelia transformation and migration involve altered cell contractile mechanics powered by an actomyosin-based cytoskeleton and influenced by cell-cell and cell-extracellular matrix interactions. A balance between contractile and adhesive forces regulates a large number of cellular and tissue properties crucial for epithelia migration and tumorigenesis. In this review, the forces driving normal epithelia transformation into highly motile and invasive cells and tissues will be discussed.

Epithelial Morphogenesis, Dynamics and Transformation

Epithelial cells show a stereotypical apicobasal polarity essential for the proper architecture and functional asymmetry of epithelial tissues.¹ Apicobasal polarity is linked to lateral cohesive contacts between neighboring epithelial cells and basal adhesion contacts between epithelial cells and structural components of a specialized extracellular matrix (ECM).¹

Through the establishment of strong adhesive interactions, normal epithelial tissues undergo restricted movements emerging from the dynamical interaction between force-generating complexes and adhesive molecules able to propagate tensile forces and stabilize intercellular and cell-matrix contacts.² In tumor development, it appears that abnormal morphogenetic rearrangements arise from a number of processes such as the loss of epithelial polarity, deregulated adhesion contacts and altered mechanical interactions between epithelia and their ECM.^{1,3}

Epithelia transformation in cancer is accompanied by structural and dynamical modifications at cell and tissue level as well as reciprocal changes in ECM properties (e.g. topology, stiffness and composition).^{4,5} Remodeling of the ECM is promoted by cellular contractility, producing motility tracks leading to enhancement of cell migration.^{4,5} Tumor formation *in vivo* is associated with stiffening of both the ECM and epithelial tissue: mammary tumor and tumor-adjacent ECM are 5 to 20 times stiffer compared to normal mammary gland, respectively.⁶

*Correspondence to: Inês Mendes Pinto; Email: ines.m.pinto@inl.int
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An ECM stiffness increase correlates with high cell traction forces and assembly of cell-ECM focal adhesions.³ In cultured mammary epithelial cells (MECs), high ECM stiffness is sufficient to induce epithelial transformation and invasion.⁷ Similar qualitative effects were observed when transformed MECs were placed on collagen-based ECM attached to a rigid matrix versus freely floating gels, suggesting that epithelial cell dynamics is regulated by ECM generated tension.⁷

Migrating cells undergo shape changes while they exert forces deforming the surrounding tissue. Tissue deformation may lead to stress buildup resisting cell motility. In order to overpower the emerging resistance, the moving cells generate mechanical forces and can actively degrade the ECM through the proteolytic action of metalloproteinases.⁴ The driving forces for epithelia migration and their dependence on cellular and extracellular mechanical properties are reviewed in this manuscript.

Contractile Force Generation and Transmission for Epithelial Cell Migration

Major sources of forces used for epithelial cell translocation include actomyosin contraction and protrusive force produced by actin polymerization. In epithelial cells, contractile actomyosin networks, (assembled by filaments of actin and myosin-II) are linked to E-cadherin and integrin based adhesion complexes,⁸ which mediate intercellular and cell-ECM force transmission and are able to translate single cell dynamics into tissue-level behaviors.⁹ Actomyosin subcellular distribution, contractile activity and coupling with adhesion complexes, overall defines epithelial morphodynamics and its mechanical interactions with the surrounding matrix.⁹

Recent findings show that hyperactivation of epithelial actomyosin components such as myosin-II motor strongly correlates with actomyosin hypercontractility, altered ECM and cell-ECM interactions and tumor proliferation.⁵ Actomyosin contractility-dependent cellular tension leads to increased production and fiber diameter of collagen, one of the major ECM structural proteins, thus promoting high ECM stiffness and faster tumor cells proliferation *in vitro*.⁵ Actomyosin contractility also plays an important role in tumor cell invasion into the ECM by different mechanisms: (1) protease-dependent mechanism, by promoting the ECM degradation through the protrusive action of invadopodia structures;¹⁰ and (2) protease-independent mechanism, by exerting contractile forces able to deform the ECM matrix.¹¹

A net translocation of single epithelial cells, within a tissue, occurs as a transition process only when forces generated by the cell are not balanced by the ECM and cell-cell adhesions, producing a nonzero net traction force.¹² In fact, formation or dissociation of an adhesion site breaks temporarily the force balance, and the cell starts to move until the net traction over all cell-ECM adhesions vanishes.² If we assume random spatial distribution of adhesion formation/dissociation sites, the cell migrates diffusively with a speed inverse to the number of engaged adhesion sites, as observed *in vitro*.¹³ Due to enlarged cell spreading area, a higher number of cell-ECM adhesion contacts on a stiffer matrix leads to a slower cell migration.²

In migrating epithelial cell sheets, cells may differentially regulate their levels of myosin-II contractility and cell-ECM mechanotransduction to promote longer-range force transmission during collective migration. How mechanical interactions with ECM and with neighboring cells regulate movements during collective migration, nevertheless, is poorly understood. The effects of polyacrylamide-based matrix stiffness (ranging from a few to tens of kPa) on sheet migration of MCF10A epithelial cells were recently analyzed.¹⁴ Migration speed, directionality and cell-cell coordination in a moving epithelial sheet were all found to increase with elevated matrix stiffness. Importantly, myosin-II contractility modulates cadherin-dependent cell-cell adhesions and matrix stiffness for epithelial sheet movement, suggesting that contractile forces regulate collective migration.¹⁴

ECM components have often an elastic modulus, typically on the order of tens of kPa, which is much higher than the reported for cells *in vitro*; although there are large variations among tissue types suggesting differences in the ECM structure.² Epithelial cells are enriched in actomyosin networks able to produce high contractile forces. Epithelial cells attached to the ECM are subject to an internal cell-autonomous stress (also called pre-stress) mediated by actomyosin based contractile forces. Therefore, the existence of the pre-stress can be inferred from the interactions of cells with the ECM while it is very difficult to measure it directly. As in muscle cells,¹⁵ pre-stress of the actomyosin-based cytoskeleton leads to cell stiffening; a linear relation between pre-stress and stiffness is observed in epithelial cells.¹⁶ The interplay between cell contractile force and ECM stiffness generates a dynamic feedback on the moving cell: the cell that pulls itself forward through a dense tissue needs to contract and adhere to the tissue. The contraction increases cytoskeletal pre-stress leading to elevated cell stiffness which, however, inhibits cell deformations and could hinder migration.¹⁶ A nonlinear feedback between cell velocity and the forces accompanying the movement determines the migration speed. This feedback mechanism is similar to the one operating during skeletal muscle contraction: generation of actomyosin based force increases intracellular resistance which leads to progressive decay of the maximum muscle contraction velocity.¹⁶ Similar feedback regulation is essential for the migration of a cell surrounded by other cells through the 3-dimensional environment of a tissue. In addition to internal cell pre-stress and stiffness, a cell moving through stiff neighbors senses their stiffness too. Thus, these neighboring cells mimic stiff ECM, with the only difference that in force transmission between

cells, integrin-type cell-ECM adhesions are replaced by cadherin-based cell-cell adhesions. Extracellular stiffness, however, is not always critical for cell migration, suggesting that at least for some migration modes cell adhesion to ECM may be insignificant or even completely dispensable.^{17,18}

Contractile Forces and Different Modes of Cell Migration

Spatially localized assembly and contraction of the actomyosin machinery contribute to a repertoire of different migratory modes⁹ by controlling different determinants as cell migration cellularity (single or multicellular, also called collective, migration). Depending on the context, single cell and multicellular movement occurs across a 2-dimensional (2D) or through a 3-dimensional (3D) ECM. Time-lapse and phenotypic analyses suggest that both single and multicellular migration modes are observed in many morphogenetic processes, tissue regeneration and tumor progression.

Similarly to individual cell motility, multicellular translocation stems from actomyosin contractility and actin polymerization, however there are few major distinctions. In multicellular migration, the epithelial cells maintain intercellular junctions both at the edges and inside the epithelial sheet. Multicellular migration is characterized by coordinated and synchronous polarization at the leading edge as well as by dynamic protrusions along or underneath the moving cell sheet.¹⁹

When cell-cell adhesion is strong enough to maintain intercellular junctions, the translocation of the inner cells with respect to their neighbors is negligible while they collectively follow signals from cells at leading edge of epithelial sheets.²⁰ The migrating group of some cancer cells has a very specific distribution of actomyosin forces which are stronger at the group perimeter where actomyosin has a band-like structure encircling the cluster.²¹ Conversely, actomyosin contraction at the cell-cell junctions is diminished to preserve these contacts (Fig. 1A). When the actomyosin force is distributed uniformly through the cluster, cell junctions are weakened, leading to the cluster breakup.²¹

Many features of the molecular mechanisms of cell-ECM interaction in individual cell migration are observed in collective cell migration, including force generation accompanying cell-ECM adhesions and formation of actin-rich protrusions.¹⁹ The mechanisms regulating polarized actin polymerization and leading to protrusion of a collective leading edge may also bear similarity to the mechanism of polarization in individual migrating cells.²² Leading edge protrusions are highly dynamic actin-based structures that respond to spatial cues (e.g., increased concentration of chemoattractants and other growth factors) by orienting the cell polarity machinery and determining the distribution of cell-ECM adhesions.²³ The force driving cell protrusions is produced by actin filament polymerization toward the plasma membrane.²⁴ In collective migration on 2D ECM, the leading row contains lamellipodia enclosing multiple cell boundaries and driving the front edge forward.²⁵ Additionally, the migrating epithelial sheet produces underneath each cell lamellipodia-based

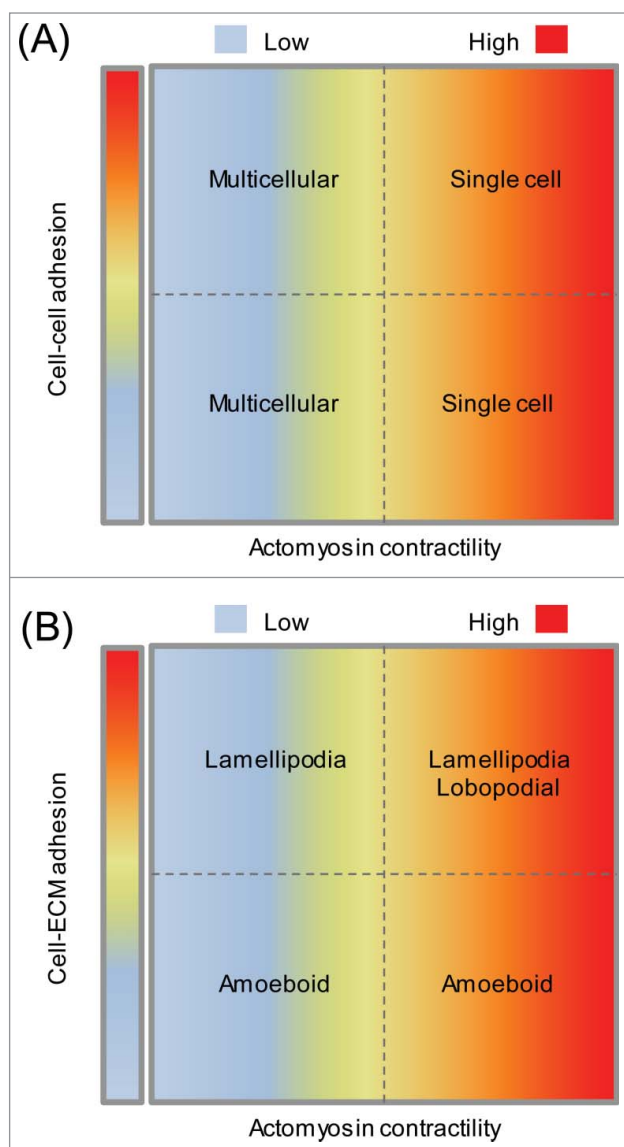


Figure 1. Dynamic balance between actomyosin contractility and cell-cell (A) and cell-ECM (B) adhesion forces determines different cell migration modes. (A) Increase in actomyosin contractility leads to disruption of the collective migration and an emergent single cell motility for both low and high cell-cell adhesion. (B) For low cell-ECM adhesion the amoeboid migration is preferred, while for the higher adhesion (and stiffness) the lamellipodia-based migration is selected, but it can be replaced by the lobopodial migration in 3D stiff environment.

protrusions exerting traction forces on the ECM. Force generation is therefore observed both in leading cells and in inner cells of the migrating sheets, suggesting that collective migration involves a synchronized multicellular translocation.²⁵

Detailed histological analysis of epithelial derived tumors reveals that most epithelial cancers have distinctive features of collective invasion into surrounding tissues.²⁶ Such collective cell migration and invasion requires a tight maintenance of cell-cell adhesion contacts. Thus, the individual or collective cancer cell motility (and possible transition migratory

patterns) is regulated through cell-cell coupling gain or loss (accompanied by downregulation of E-cadherin). A mild decrease in cell-cell adhesion with some cell-cell junctions still intact can lead to multicellular strand-like migration.²⁵ This transformation from an epithelial phenotype to lamellipodia-based (also called *mesenchymal*) cell migration²⁷ is commonly referred as incomplete epithelial-mesenchymal transition (EMT).²⁸ Loss of E-cadherin within cell-cell junctions occurs during complete EMT when a group of cells breaks into individual mesenchymal invading cells both *in vivo* and *in vitro*.²⁰ Hyperactivation of actomyosin contractility²⁰ and inhibition of $\beta 1$ integrin²⁹ also leads to individual cell separation from primary melanoma explant cultures, followed by amoeboid migration (a process known as collective-amoeboid transition).^{19,29,30}

Unlike in mesenchymal cells, cortical actomyosin distribution in *amoeboid* cells is isotropic and uniform on average, with local and temporary perturbations unsynchronized both in time and in space.³⁰ These cells are characterized by the formation of actin-free blebs due to separation of the membrane from the cortex driven by either depletion of the cortex-membrane linker proteins or by local inward movement of the cortex. These two mechanisms of bleb formation may coexist and enhance each other.³¹ It is important to note that bleb formation is critically dependent on the level of actomyosin contractility as local myosin-II activation can promote an increase in the intracellular poroelastic hydrostatic-based pressure leading to cortex decoupling from the plasma membrane and blebbing nucleation.³² The tendency for amoeboid cell migration correlates with low traction forces and correspondingly low adhesion to the ECM. Therefore elevated actomyosin contractility through bleb formation provides a mechanism for invasive tumor cells to migrate on poorly adhesive substrates. The plasticity of tumor cells allows them to use a more refined strategy to optimize their motility in changing environments and thus promote tumor growth. For example, Walker carcinoma cells probe ECM adhesion level and dynamically switch between the mesenchymal and amoeboid modes.³³ The transition from lamellipodia to blebs is very fast (in seconds) and is promoted by an increased cortical contractility through elevated myosin-II activity.³³ The dynamic switch from bleb back to lamellipodia is triggered by Rac1 activation which enhances protrusive actin polymerization and decreases contractility.³³ Interestingly, elevated contractility also limits lamellipodia outgrowth indicating that actomyosin contractility plays a critical role in the switching between the 2 modes (Fig. 1B).

Nevertheless, in 3D matrigels, breast tumor cells are still able to migrate without the requirement of any lamellipodia based protrusions or bleb nucleation.³⁴ The transition between symmetric and asymmetric actomyosin cortical distribution and contractility correlating with the transition between non-migratory to migratory phenotype can be explained by a symmetry breaking model.³⁵ In this model dynamical instabilities of the cortex leading to steady-state cortical flows can appear spontaneously without any apparent external regulatory signals. Dynamic instabilities arise from actomyosin contractility controlled by myosin-II cortical flow and free diffusion. Myosin-II cortical flow

converges to one cell pole where the cortex thickens and contributes to the generation of a self-propulsive force.³⁵

In addition to these 2 migratory modes, a novel type of cell motility was recently reported as *lobopodial* migration in a stiff 3D elastic matrix of dermal explants with high level of actomyosin cortical contractility driven by RhoA hyperactivation at the cell leading edge³⁶ reflecting an actomyosin distribution different from both lamellipodial and amoeboid modes. Lobopodium is a blunt cylindrically shaped protrusion created by an intracellular pressure increase in 3D elongated cells; lobopodial-based protrusions can evolve into lamellipodia when ECM properties are altered or actomyosin contractility is reduced.³⁶ Notably, lobopodial cells rely on cortical actomyosin contractility like amoeboid cells do, but lobopodial migration requires cell-ECM adhesion as required for the lamellipodial mode (Fig. 1B).³⁶

Regulation of cell migration is a complex biomechanical process involving many interacting components. In lamellipodial-based mode, cell migration speed is regulated by a dynamical feedback between actomyosin contractility and adhesion.³⁷ In fact, PtK1 epithelial cells provide an example of lamellipodia-based cell migration in fibronectin-based ECM with a non-monotonic biphasic velocity of migration as a function of adhesion strength: at low and high cell-ECM adhesion slower migration is observed, while intermediate cell-ECM adhesion correlates with faster migration.³⁷ A simple descriptive model was proposed to explain this phenomenon: When adhesion is high it cannot be overpowered by the contraction force; at low adhesion, weak focal adhesions are torn off from the ECM by contraction at both the cell front and rear; an optimum speed is reached for intermediate adhesion values, when traction generated at the front correlates with cell rear detachment.³⁷

A mechanical model describing how tumor cells optimize migration strategy in different ECM environments was developed recently to analyze the role of blebs and actin polymerization protrusions according to levels of cell adhesion and contractility.³⁸ The actomyosin cortex and the outer cell membrane were described as the set of point agents linked by the viscoelastic elements resisting to compression, stretching and bending. Actin polymerization based protrusions were initiated randomly with the membrane pushed forward by a constant force applied to the protrusion tip. The model cell locally assembles adhesion contacts to the ECM and cortical contractile forces are allowed to act on the ECM. Several types of ECMs were considered – a surface, a confined topologically continuous (channel-like) and confined discontinuous environments. The major model predictions are: (1) in the absence of actomyosin contractility, cell migration directionality is determined solely by the polarity of actin protrusions; (2) for medium and high adhesion levels, cell migration speed correlates with the level of contractility independently of the type of ECM environments or protrusion mechanism; (3) for low adhesion levels, the relation between contractility and cell migration speed is more complex and depends on both ECM topology and protrusion mechanism; (4) finally, in the non-adhesive case, cell migration is possible only in the confined discontinuous environment independently of protrusion mechanism. These behaviors are predicted for the

polarized cell with preferential protrusions or blebs at the front edge and localized contractility at the rear edge.³⁸

Another prediction of the model accounts for geometric parameters in confined environments. For the channel-like confinement when both blebs and protrusions are activated, the dependence of cell migration speed on the contractility level can be approximated by a monotonous function, with the slope of this function changing from negative to positive values when the channel width decreases. This result can be explained qualitatively as follows: when the cell migrates on the inner surface of a wide channel an increased level of contractility leads to cell detachment from the ECM reducing the speed. When the cell is set into a narrow channel, the probability of such detachment drops, and the narrower the channel the lower the likelihood of detachment, which eventually leads to positive correlation between contractility and cell migration speed.³⁸

However, at small confined *in vitro* environments, alternative cell migration strategies can emerge independent of both actomyosin contraction and actin polymerization-based forces. A recent study reveals hydrostatic and osmotic-based cell propulsion forces driving breast epithelial tumor cell migration through 3 μ m-wide engineered channels.³⁹ In this scenario, cell translocation is driven by polarized distribution of Na⁺/K⁺ pumps at the front cell edge membrane, followed by cycles of water and ions inflow (at the cell front edge) and outflow (across the cell trailing edge membrane).³⁹ It remains to be seen to which extent this newly identified migration mechanism can recapitulate tumor cell dynamics *in vivo*.

Summary

There is an emergent interest in understanding the mechanics of actomyosin contractility and its implication in epithelial cell migration during development and tumorigenesis. How cells organize similar actomyosin structural components in order to rapidly switch between different migration modes remains an unresolved question. To date, no quantitative experimental analysis and/or mathematical models could explain such dynamic reconstruction. Modeling of contraction-based epithelial cell migration requires an integrative description of force generation: (1) Detailed subcellular analysis of actomyosin assembly and disassembly on a spatial scale of 10 to 1000 nm determined by the size and length of their components (myosin-II molecules and actin filaments);⁴⁰ (2) Temporal analysis of actomyosin contraction defined by the kinetics of myosin-II interactions with actin filaments; (3) Integration of nanoscale actomyosin contraction defining parameters into a macroscopic scale considering the epithelial cell size and the time required for its translocation; and (4) Quantitative analysis of single cell contraction influence in tissue behavior considering the dynamics and rheological properties of cell-cell and cell-ECM interactions. Therefore, a biophysical model able to predict and describe epithelia contraction-based migration *in vivo* requires a complex multiscale approach explaining contractile force generation and transduction from subcellular actomyosin domains into cell and tissue dynamics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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