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Review

Mechanobiology of cell migration in the context of dynamic two-way cell–matrix interactions

Nicholas A. Kurniawan [a,b], Parthiv Kant Chaudhuri [c], Chwee Teck Lim [c,d,*]

[a] Department of Biomedical Engineering, Eindhoven University of Technology, P.O. Box 513, 5600MB Eindhoven, The Netherlands
[b] Department of Systems Biophysics, FOM Institute AMOLF, Amsterdam, The Netherlands
[c] Mechanobiology Institute, National University of Singapore, Singapore
[d] Department of Biomedical Engineering, National University of Singapore, Singapore

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ABSTRACT

Migration of cells is integral in various physiological processes in all facets of life. These range from embryonic development, morphogenesis, and wound healing, to disease pathology such as cancer metastasis. While cell migratory behavior has been traditionally studied using simple assays on culture dishes, in recent years it has been increasingly realized that the physical, mechanical, and chemical aspects of the matrix are key determinants of the migration mechanism. In this paper, we will describe the mechanobiological changes that accompany the dynamic cell–matrix interactions during cell migration. Furthermore, we will review what is to date known about how these changes feed back to the dynamics and biomechanical properties of the cell and the matrix. Elucidating the role of these intimate cell–matrix interactions will provide not only a better multi-scale understanding of cell motility in its physiological context, but also a more holistic perspective for designing approaches to regulate cell behavior.

Contents

* Corresponding author at: Department of Biomedical Engineering, Faculty of Engineering, National University of Singapore, 4 Engineering Drive 3, 117583 Singapore. Tel.: +65 6516 7801; fax: +65 6872 3069.
E-mail addresses: kurniawan@tue.nl (N.A. Kurniawan), a0095421@nus.edu.sg (P.K. Chaudhuri), ctlim@nus.edu.sg (C.T. Lim).

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1. Introduction

Cell migration is crucial in many biological functions, ranging from embryonic development, morpho- and organogenesis, immune response, to wound healing. It is also involved in pathophysiological processes such as those occurring in cardiovascular diseases and cancer metastasis. During these migration processes, cells have to navigate through extracellular space with a wide variety of microstructure and biochemical properties (Charras and Sahai, 2014). This extracellular matrix (ECM) ranges from 2D surfaces such as the basement membrane to complex 3D environment such as connective tissues. In addition to providing the scaffold that support tissue integrity, the ECM functions as attachment substrate, signaling medium, and movement'tracks', but at the same time it can also act as a physical barrier for the cells (Lu et al., 2012). The role of the ECM in modulating cell migration characteristics, both at the molecular and phenomenological levels, is increasingly recognized, although many aspects of this dynamic interaction are still underappreciated.

Cell dynamics, including migration, is achieved by integrating internal cues within the cell and external cues from the environment (Fig. 1). In this review, we will briefly summarize the environmental cues from the ECM that guide cell migration, how cells are able to interpret and respond to these cues, the effects of the resulting cell dynamics arising from the biomechanical properties of the ECM, and how these effects feed back to influence cell behavior. We will in particular focus on the biomechanical changes in the cells and the ECM that accompany these dynamic interactions. Doing so, we aim to highlight the importance of considering the dynamics of cell–ECM interactions and therefore provide a better understanding about cell motility in its biomechanical context.

2. External cues guiding cell migration

The migratory characteristics of cells is motivated but also constrained by external cues from the environment. We broadly categorize these cues as physical/mechanical and biochemical cues.

2.1. Physical and mechanical cues

Cells are only able to move as much as their surrounding allows them to. Since cell motility necessitates significant changes in cell shape, geometric *confinement* can affect many parameters of cell migration. In 3D connective tissues, the confinement effect is largely defined by the porosity of the matrix that the cell penetrates. When the pores are smaller than cell size, the cell needs to deform to squeeze through the confined environment. The smaller the pore, the harder it is for the cells to migrate. *In vitro* hydrogels used to study 3D cell migration typically has pore sizes ranging from nanometers for synthetic flexible polymers to micrometers for reconstituted extracellular biopolymers and hundreds of micrometers for electrospun or 3D-printed scaffolds. Moreover, cell's resistance to deformation, typically measured as cell stiffness, naturally also plays a role. Lower cell stiffness or high deformability (down to ~500 Pa *vs* ~2 kPa for normal cells) is correlated with metastatic potential (Smelser et al., 2015; Xu et al., 2012) and has been exploited as a mechanical biomarker for rapid cell phenotyping (Otto et al., 2015). A recent study has reported that the size and deformability of the nucleus are the limiting factor to cell's ability to squeeze through tight pores, with pore sizes of 1–2 μm appearing to be the physical limit (Wolf et al., 2013). It is important to note that this limit is in turn determined by the stiffness of subnuclear constituents such as the nuclear lamina (Harada et al., 2014). In contrast, on 2D surfaces such as that found on a culture dish, the cell has a much wider space to explore and the migration is therefore often dominated by broad, flat protrusions called lamellipodia that are driven by the polymerization and treadmilling of branched actin networks (Lauffenburger and Horwitz, 1996). Migration in environments with more complex confinements and geometries such as tubes, channels, and discontinuous surfaces naturally requires more complex machineries that involve combined effects of cell contractility, substrate topography, and surface adhesion (Tozluoğlu et al., 2013; Wilson et al., 2013).

The architecture of the physiological ECM is arguably even more complex and diverse and serves as a key regulator of various cell functions (Kim et al., 2012). Substrate *topography* such as nanogrooves and ridges have provided experimental evidence that cells can preferentially orient and elongate along nanogrooves (Yim et al., 2005) and migrate parallel to nanoridges (Diehl et al., 2005). This might bear resemblance to 1D-like topology of ECM fibers, which can form tracks that guide cell migration (Provenzano et al., 2006). In addition to influencing the direction, substrate topography also affects the speed of cell migration (Jeon et al., 2010). Interestingly, this effect is modulated by the density of the nanopatterned ridges and is observed in both individual and collective migrations of cells (Kim et al., 2009), thereby suggesting a complex interplay between length-scale dependent topology sensing, cell–substrate adhesion, and cell–cell contact.

Matrix *stiffness* is another important factor that needs to be taken into account. The stiffness of tissues *in vivo* ranges many orders of magnitude, from around 100 Pa in adipose and brain tissues to MPa and GPa in bones (Discher et al., 2005). The stiffness of the matrix determines how much the cell can deform its surrounding and therefore plays an important role in governing the ability and efficiency of cells to migrate. Not unexpectedly, alterations in matrix stiffness is associated with progression of diseases including cancer, fibrosis, and atherosclerosis (Handorf et al., 2015). In fact, the macroscopic stiffness of breast tumors has long been used as a diagnostic tool and is strongly correlated with local recurrence and metastasis (Fenner et al., 2014). The migratory speed of tumor cells in 3D matrices is indeed strongly affected by matrix stiffness in a non-monotonic manner due to the balance of forces between cell contractility and matrix deformability (Zaman et al., 2006). The coordinated action of actomyosin-mediated cell contractility on matrix adhesion thus effectively functions as a mechanosensing unit (Trichet et al., 2012). Moreover, it has been shown that on a substrate with a stiffness gradient, cells preferentially migrate towards the stiffer areas in a process known as durotaxis (Lo et al., 2000). This results from the cell's ability to sense local substrate stiffness and has been suggested to play a role in tissue repair (Vincent et al., 2013).

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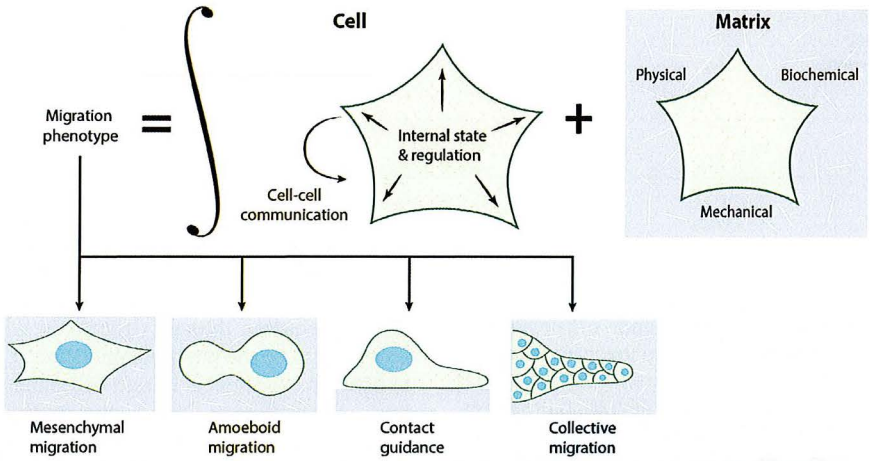

Fig. 1. An illustration of the dynamic interactions between the cell and the matrix during cell migration. While navigating through the matrix, the cell continually integrates physical, biochemical, and mechanical cues from its internal biomolecular regulation, from other cells, and from the matrix, resulting in different phenotypes of migration. The cell can also adapt to particular matrix conditions and display plasticity between these different phenotypes.

2.2. Biochemical cues

In addition to these mechanical communications, cells in the tissue also interact by secreting and receiving biochemical signals of various soluble factors like chemokines, matrix metalloproteinases (MMPs) and growth factors, which can induce changes in cell migratory behavior.

Chemokines are specialized chemotactic cell-secreted signaling proteins (*cytokines*) that stimulate directed cell movement along a concentration gradient of the ligand. They are triggered by various inflammatory cytokines, growth factors, and pathogenic cues (Rossi and Zlotnik, 2000). Infiltration of leukocytes to the wound sites is a prime example of tightly-controlled chemokine-mediated process. Chemotaxing leukocyte elongates, polarizes, and undergoes random migration under uniform chemokine stimulation, but in the presence of chemokine gradient, they migrate towards higher chemoattractant concentration in a directed manner (Devreotes and Zigmond, 1988). *In vivo* two-photon microscopy revealed a chemokine gradient across 100 μm inside lymph nodes that triggered migration of B cells towards the follicle edge (Allen et al., 2007). Single cell motility in the presence of a chemokine gradient has been observed during developmental processes in zebrafish and mouse model (Herpin et al., 2008) and during directed primordial germ cell movement (Molyneaux et al., 2003). Chemokine gradient also plays a significant role during cancer metastasis. Melanoma and glioblastoma cells secrete chemokines that attracts leukocytes including T cells and neutrophils to the invasion sites, which can have both positive and negative effects on metastatic dispersion (Mrowietz et al., 1999). The specific secondary locations for breast cancer metastasis have also been attributed to attraction of CXCR4-expressing tumor cells to target organs including lung, liver, and bone that expresses CXCL12 ligands (Muller et al., 2001).

Matrix metalloproteinases (*MMPs*) can exist in active or inactive state and form a crucial part of the migration mechanism of cells through 3D matrix. MDCK epithelial cells express MT1-MMP and form a branched tubular structure when they invade through 3D collagen gel in presence of hepatocyte growth factor (HGF) (Hotary et al., 2000). During wound healing, MMP-1 binds to keratinocytes *via* $\alpha 2\beta 1$ integrin and helps in the motility of these cells through the collagen matrix. The degradation of collagen matrix by MMP-1 is crucial for the motility of keratinocytes, as cells are unable to move through a mutant collagen gel that cannot be cleaved by MMP-1 (Pilcher et al., 1997). During cancer metastasis, most of the activated forms of MMPs are expressed at the junction between the tumor–stroma interfaces where active invasion occurs (Sternlicht and Bergers, 2000). Malignant cells can stimulate the stromal cells in a paracrine manner to secrete most of the MMPs (McKerrow et al., 2000). MMPs 1, 2, 3, 9 and 14 play a crucial part in degrading the physical barrier of the ECM for tumor invasion and enhancing the angiogenic infiltration of endothelial cells in the metastatic site (Sternlicht and Bergers, 2000).

Growth factors are soluble molecules released by the cells in the tissue microenvironment that are responsible for controlling the dynamic communication between the cell and the matrix. Some of the major growth factors involved in cell motility regulation include fibroblast growth factor (FGF) (Heinzle et al., 2012), epidermal growth factor (EGF) (Quesnelle et al., 2007), platelet-derived growth factor (PDGF) (Shih and Holland, 2006), and transforming growth factor (TGF)-β (Samanta and Datta, 2012). During wound healing, platelets degranulate and secrete growth factors including EGF, PDGF, and TGF-β. FGF regulates the motility of convergent extension by reorganizing the cytoskeletal structures and polarizing the cells (Bottcher and Niehrs, 2005). Interestingly, FGFs have been reported to perform as both chemoattractant and repellant during gastrulation (Yang et al., 2002). PDGF and cytokines such as IL-1 act simultaneously to attract neutrophils to the injured site to remove bacterial contamination (Hantash et al., 2008). The tumor–stromal cell interaction leads to the secretion of soluble factors for triggering growth and metastasis of cancer cells. Endocytosis of TGF-β receptor has been implicated in metastatic spread (Hu et al., 2013). Mutation of TGF-β receptor delays the internalization of receptor and subsequently leads to sustained TGF-β signaling and acquisition of higher invasive phenotype in human oral squamous cell carcinoma (Park et al., 2012). Internalization of activated FGF receptor is associated with increased cell migration and tumor progression. FGF induces endocytosis of FGFR1 and E-cadherin and this results in Epithelial-Mesenchymal Transition (EMT) of the cells (Bryant et al., 2005).

Soluble signals are communicated from the same cells ("*autocrine signaling*") as well as from other cells in the stroma ("*paracrine signaling*"). The stromal cells mainly comprise fibroblasts, macrophages, endothelial cells, and numerous inflammatory and immune cells (Hoelzinger et al., 2007; Joyce, 2005). *Fibroblasts* are normally inactivated, but during fibrosis, wound healing, and cancer metastasis, they become activated and are responsible for tissue remodeling and secretion of various biochemical factors. Exosomes secreted by fibroblasts have been reported to play an important role in stimulating breast cancer cell motility and metastasis (Luga et al., 2012). *Endothelial cells* are triggered in the

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presence of melanoma and glioma cells to secrete chemokines that direct the locomotion of cancer cells towards the lymphatic vessels (Ramjeesingh et al., 2003). Additionally, endothelial cells can also stimulate tumor cells to secrete several growth factors, chemokines, and MMPs to facilitate matrix degradation and metastatic spread (Hoelzinger et al., 2007; Ramjeesingh et al., 2003). *Tumor-associated macrophages* (*TAM*) have been associated with increased metastatic dissemination and poor prognosis (Pollard, 2004). TAM and cancer cells reciprocally stimulate each other in a tumor environment. TAMs secrete EGF and express colony-stimulating factor 1 (CSF-1) receptor, and interestingly cancer cells respond to the secreted EGF and also produce CSF-1 (Wyckoff et al., 2004). Macrophages can also degrade the ECM by actin-rich structures like podosomes and thereby releasing chemotactic peptides to favor chemotaxis of malignant cells (Mott and Werb, 2004).

3. Mechanosensing and cell adaptation

At the cell level, the effects of the various physical and mechanical cues from the environment have been well documented. The cell senses the cues at the molecular level and responds to them by actively altering its migratory machinery and thereby migrational phenotype.

3.1. Cell mechanosensing

Focal adhesions are special macromolecular structures that link the ECM ligands on the substrate outside the cell with the cytoskeleton inside the cell. As the physical linkages between the cell and the ECM, focal adhesions have received tremendous attention in unraveling cellular mechanosensing machinery (Geiger et al., 2009; Grashoff et al., 2010). One particular transmembrane receptor that mediates focal adhesion dynamics is *integrin*. Integrin-mediated adhesions act as signaling hubs for a multitude of regulatory proteins controlling diverse cellular functions (Zaidel-Bar, 2013). Single-molecule force-spectroscopy measurements have started to reveal insightful mechanosensitive properties of integrin–ECM bonds such as catch-bond behavior (Friedland et al., 2009; Kong et al., 2009). External force can activate integrins (Sawada et al., 2006) and influence formation of focal adhesion (Riveline et al., 2001), indicating integrin's involvement in mechanosensing. Moreover, activation of different types of integrins leads to significant changes in traction force generation on 2D surfaces (Lin et al., 2013; Schiller et al., 2013) and affects ECM synthesis in 3D environments (Humphrey et al., 2014), further suggesting that cells can actively regulate their dynamic physical and chemical interactions with the ECM simply by modifying integrin expression profile. In light of these important roles in regulating cell–cell and cell–matrix adhesions, therapeutic intervention targeting integrins holds a promising potential in inhibiting tumor progression and cancer metastasis. The main challenges are decoupling competing factors that are co-regulated by integrins, such as tissue stiffness, cross-linking, and altered matrix adhesion, as well as identifying the specific functional pathways and the types of integrins involved (Levental et al., 2009; Paszek et al., 2005; Ramirez et al., 2011). In addition, the morphology and dynamics of integrin-mediated cell–matrix adhesions in 3D environments is complicated by other physical factors such as the fiber topography, which generally result in reduced adhesions (Kubow and Horwitz, 2011).

Mechanosensation can also be mediated by the highly dynamic actin *cytoskeleton*. With the help of a variety of actin-related proteins, actin filaments can organize into diverse architectures in the cell, producing branched networks in lamellipodia, parallel bundles in filopodia, and antiparallel bundles in contractile fibers (Blanchoin et al., 2014). The cooperation of actin and its associated motor protein, myosin, in antiparallel configuration results in cell traction forces ("actomyosin contractility") that helps maturation of focal adhesions and reinforces actin anchoring (Ciobanasu et al., 2014), as well as unbundling and depolymerization into individual filaments (Haviv et al., 2008) that are important in the long-range coordination of actin restructuring across the cell during cell motility (Wilson et al., 2010). It has been recently reported that a balance between actin network connectivity (*via* crosslinkers) and activity (*via* myosin) governs the range and induction of actin contractility (Alvarado et al., 2013). On 2D surfaces, myosin-mediated contractility tunes the dynamics of cyclic lamellipodial protrusion, adhesion, and retraction on the leading edge of the cell, which facilitate cell mechanosensing (Giannone et al., 2007). The contractile actomyosin bundles are called *stress fibers*. Substrate stiffness governs the prominence and maturation of stress fibers in myotubes (Geiger et al., 2009) and exogenous stretching of these stress fibers using optical tweezers has been reported to activate mechanosensitive channels in endothelial cells (Hayakawa et al., 2008), further emphasizing the role of stress fibers in cellular mechanosensing. It has also been suggested that the degree of actin cross-linking, which is influenced by substrate stiffness, can in turn regulate the overall cell stiffness, thus allowing the cells to actively adapt their stiffness to that of the environment (Solon et al., 2007). The direct role of stress fibers in cell migration is however still elusive, partly because stress fibers are absent in many highly motile cells and in cells embedded in 3D environment (Tojkander et al., 2012). Moreover, the role of other cytoskeletal components, such as microtubules and intermediate filaments, as well as their interactions with actin and between each other in mechanosensing has only started to be systematically explored (Huber et al., 2015).

3.2. Migration modes and cell plasticity

Cell migrational phenotype can be broadly categorized into two modes: (1) individual cell migration mode that comprises mesenchymal and amoeboid types of migration and (2) collective cell migration mode, where intercellular junctions are maintained and cluster of cells moves in a coordinated manner.

3.2.1. Mesenchymal migration

This mode of migration is mainly observed in fibroblasts and tumors of epithelial (carcinomas) and connective tissue origin (sarcomas). The characteristic features of this type of migration are an elongated morphology, increased traction forces generation, and highly polarized cytoskeletal contraction (Friedl and Wolf, 2003). At the leading edge, cells form a lamellipodial protrusion and maintain integrin-mediated focal contact with the matrix. In dense 3D matrix, MMPs are accumulated at the leading edge of the cell in an integrin-dependent manner and this helps in cleavage of the ECM to generate a path for the migrating cells to overcome obstructions from the tissue barriers (Wolf et al., 2003a). Due to the involvement of strong matrix adhesion, mesenchymal migration is relatively slow (0.1–0.5 μm/min *in vitro*) (Pankova et al., 2010). Metastatic cancer cells also use this type of migration when they escape from the primary tumor after undergoing EMT, whereby cell–cell adhesion and apical–basal polarity are lost and the cells become more invasive.

3.2.2. Amoeboid migration

So called because of the rounded amoeba-like morphology that the cell adopt while migrating, this mode is typically used by highly motile cells such as dendritic cells, leukocytes, hematopoietic stem cells, and some cancer cells (Friedl and Weigelin, 2008). The amoeboid migration is associated with reduced

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intrinsic polarity and focal adhesions (Lammermann and Sixt, 2009). This mode can be further classified into two types based on the migratory structures involved: propulsion of blebs (Charras and Paluch, 2008) and projection of actin-rich filopodia (Sabeh et al., 2009). Since there is less involvement of integrin-mediated adhesions, cells can move across different tissue microenvironments regardless of the chemical nature of the matrix (Wolf et al., 2003b). Amoeboid migration is consequently much quicker than mesenchymal migration (2–20 μm/min) (Pankova et al., 2010), and is used by cancer cells to escape chemotherapeutic agents targeting integrin mediated pathways (Friedl and Wolf, 2010).

3.2.3. Collective migration

This type of migration occurs during embryonic developmental processes such as neural tube closure, sheet migration in blastoderm and ectoderm, border cell migration during drosophila development, and in tumors of epithelial origin in which cell–cell contacts are preserved (Vedula et al., 2013b). The characteristic feature is a strong intrinsic polarity of the leader cell, which makes way through the ECM for the subsequent follower cells (Friedl and Gilmour, 2009). Collective migration occurs on both 2D surfaces (migration of epithelial sheet during wound closure) (Vaughan and Trinkaus, 1966) and in 3D environment as branches in mammary gland, as tubes during vascular sprouting (Gerhardt, 2008), or as strands or clusters during migration of lateral line in fish (David et al., 2002). In 2D sheet migration, the leader cells mainly use lamellipodia at their leading edge and exert traction force *via* actomyosin contraction. By contrast, in 3D condition, the leader cells extend filopodia and pseudopodia-like structures to drive the movement of the entire group of cells (Kramer et al., 2013). Collective migration can also play a key part during cancer metastasis. It has been reported, both *in vivo* and *in vitro*, that melanoma (Friedl, 2004) and colon carcinoma (Nabeshima et al., 1999) cells maintain their E-cadherin-mediated cell–cell junctions and move as a functional unit. The leader cells undergo EMT and have mesenchymal characteristics, generating forward traction forces and secreting MMPs to degrade the matrix (Khalil and Friedl, 2010). In another class of invasion, distinct leader cells are not obvious and a blunt-bud like tip moves through the matrix (Ewald et al., 2008).

Collective migration of cells is especially interesting as it includes an additional set of cues that arise from the direct contact and communications between the cells. Recent studies have observed that collective cell migration is governed by various cues such as adhesion strength between cells (Kabla, 2012), contact inhibition of cellular movement (Desai et al., 2013), geometrical constraint from the tissue and the substrate (Doxzen et al., 2013; Vedula et al., 2012), traction force applied by the cell on the substrate (Style et al., 2014b), and cell density (Duclos et al., 2014). Many technologies have been developed to quantify the mechanical response of the cells under *in vitro* experimental conditions. The effect of different tissue geometries and shapes can be investigated using microcontact printing and scratch-wound assays (Vedula et al., 2013a). Recently, we fabricated alternative stripes of fibronectin coated and non-adhesive regions (separated by $>100\,\mu m$) to mimic the discontinuity of the underlying ECM in normal physiological or diseased condition (Vedula et al., 2014). Interestingly, we observed that keratinocytes exert forces over the fibronectin-coated region ($\sim$1 kPa traction force at the leading edge) and thereby collectively pull the monolayer over the non-adhesive region in the form of multicellular bridges. However, MDCK epithelial cells do not form suspended multicellular bridges under similar experimental set up due to their weak cell–cell adhesion, therefore highlighting the importance of the adhesion strength between the cells in the collective multicellular response. In another recent study we observed that circular non-adhesive gap closure depends exclusively on the supracellular actomyosin contractility of the cells in proximity to the gap edge (Vedula et al., 2015). This study highlights the importance of contractile mechanical forces produced by large-scale actin reorganization during epithelial gap closure. The forces applied by the individual cells within the migrating sheet (generally tens to hundreds of nanoNewtons) has been quantified using micropillar arrays (Du Roure et al., 2005a; Saez et al., 2005), laser ablation of a particular region within the tissue (Shen et al., 2005), traction force microscopy (TFM) (Style et al., 2014b), fluorescence resonance energy transfer (FRET) biosensors (Grashoff et al., 2010), or by introducing cell-sized micro-droplets with defined mechanical properties within a tissue (Campàs et al., 2014). Recently, it has been observed that higher tissue curvature induces leader cell formation by generating greater traction forces (150 Pa for high curvature in comparison to <100 Pa for low curvature) and enhanced stress fiber formation (Rausch et al., 2013). At the sharp concave edges, the actin cables are discontinuous and this leads to the release of the constraint and generation of leader cells at those locations. In a growing tissue, cells sometimes form clusters of 150–200 μm that generate independent vortices within the migrating sheet and decreases the expansion capacity (Vedula et al., 2012). Interestingly, when the monolayer moves into a narrower confinement, the vortices disappear and the cells tend to migrate with a higher velocity (velocity increases from 20 to 40 μm/h on reducing the channel width from 400 to 20 μm respectively for MDCK cells). Methods have also been recently developed to perform quantitative measurements of kinematic parameters (*e.g.*, maximum and average cell motility rates) as well as cell forces of cell colonies (Serra-Picamal et al., 2015; Topman et al., 2012, 2013), which are useful in comparing the effect of culture conditions such as pH, temperature, and glucose level on collective cell migration.

3.2.4. Plasticity between different modes of migration

Intriguingly, migrating cells can interchange between various types of migration in adapting to the dynamic mechanical and biochemical cues from the microenvironment. The balance between Rho and Rac signaling largely determines the inter-conversion between mesenchymal and amoeboid migration modes. Rac activation leads to mesenchymal migration whereas activation of RhoA/ROCK promotes amoeboid migration (Sahai and Marshall, 2003). Cells can also switch into different phenotypes while migrating from a 2D surface to a 3D matrix. The well spread-out 2D morphology shifts towards a spindle-shaped mesenchymal phenotype with vertical protrusions in a 3D environment (Alt-Holland et al., 2008). In another type of transition, primary dermal fibroblast switches between lamellipodia- and lobopodia-based migration in linear elastic 3D materials in response to serum or PDGF and glucose. Lobopodia are characterized by blunt cylindrical protrusions, strong cell–matrix adhesion and greater actomyosin contractility (Petrie et al., 2012). Cancer cells also use a number of different transition phenotypes to rescue themselves from adverse microenvironmental conditions including chemotherapeutic agents. Blocking of MT1-MMP leads to switching from protease-dependent mesenchymal mode to protease-independent amoeboid migration that helps fibrosarcoma cells to squeeze through the ECM pores (Wolf et al., 2007). Inhibiting β1 integrins leads to loss of cell–ECM adhesion and switching to integrin-independent amoeboid mode (Friedl et al., 2004). Mechanical cues from the microenvironment including matrix stiffness, porosity, confinement, and density can also plays a crucial part in regulating the dynamic transition between different migratory modes. In higher confinement and in the absence of substrate adhesion, cells switch to a faster amoeboid mode with increased cellular deformability (Liu et al., 2015; Tozluoğlu et al., 2013). Collective migrating cells can also detach from the multi-

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cellular cohort and continue their movement as a single cell using amoeboid mode (collective-to-amoeboid transition (CAT)). In higher 3D collagen density (reduced matrix pore size), melanoma cells and fibrosarcoma preferentially migrate collectively through the matrix. However, lower collagen density (increased pore size) leads to breaking out of single cells from the multicellular group and further migration as single cells (Haeger et al., 2014). Additionally, inhibiting β1 integrins also induces CAT in human melanoma explants (Hegerfeldt et al., 2002). These examples strongly emphasize the capability of cells to sense and adapt to environmental factors and local perturbations by exploring migration strategies that are normally suboptimal. Importantly, the ability of cells to regulate their migration mode implies that, even within the same cells, the primary migration machinery can change depending on the ECM microenvironmental conditions, and thus strategies to externally regulate cell migration (*e.g.*, in cancer metastasis) also need to be optimized for each ECM (Sun et al., 2014b).

4. Cell-induced ECM remodeling

The ECM itself is not just a static scaffold; rather, it is highly dynamic and undergoes continual physical and chemical remodeling. Cells actively modify their mechanical environment by translocating the fibers in the ECM, degrading the surrounding matrix, and also secreting its own matrix (Fig. 2). All of these can result in dynamic changes in the composition, stiffness, and architecture of the ECM, which are further exaggerated during the progression of pathological processes such as in cancer and fibrosis.

4.1. Physical remodeling

Cell traction forces are transmitted to the ECM, resulting in changes in ECM density, stiffness, and architecture. Cell compacts their surrounding gel, resulting in irreversible and anisotropic pericellular matrix (Fernandez and Bausch, 2009). As shown by mapping the local cell-induced matrix remodeling, the ECM fibers surrounding the cell are remodeled in a non-homogeneous, myosin-dependent manner that facilitates the direction of cell migration (Bloom et al., 2008) and that corresponds to the local forces exerted by the cell (Notbohm et al., 2015). Accumulation of traction forces of a population of cells within collagen gels results in global contraction of the gels (Grinnell and Petroll, 2010), suggesting that cell traction introduces internal prestress in the matrix. Indeed, it has been shown that the presence of cells leads to global stiffening of cell-seeded fibrin gels, which does not happen when actomyosin contractility is inhibited (Jansen et al., 2013). Moreover, a recent study showed that contractility-mediated pericellular fiber alignment results in *local stiffening* (up to two-fold increase in moduli) of the matrix mechanical properties at the leading edge of the cell (Wong et al., 2014), which may further promote cell motility. Interestingly, when the same experiment was done on synthetic PEG-based hydrogels with pore sizes much smaller than cell size (nm-scale), the cells fluidize the local matrix (Schultz et al., 2015), presumably leading to *local softening* instead. These experiments corroborate the ability of cells to mechanically and dynamically adapt and respond to their immediate microenvironment.

Collagen fiber orientation and architecture also undergo significant physical remodeling during malignant transformation. In normal parenchyma, collagen fibers are randomly oriented in an isotropic manner, whereas in malignant transformation, the fibers appear in an organized and anisotropic arrangement (Goetz et al., 2011). Cancer cells are found in clusters of linear collagen fibers nearby blood capillaries (Ingman et al., 2006). Additionally, using intravital microscopy it was observed that cancer cells preferentially migrate along these aligned fibers to favor invasion and intravasation into blood vessels (Condeelis and Pollard, 2006). *In vitro* studies have also observed that fibroblasts derived from malignant tissue generate linear and parallel alignment of ECM fibers (Goetz et al., 2011). The altered ECM fiber density plays an important part in regulating immune cell movement. T-cell migration is favored by loose arrangement of collagen and fibronectin, whereas dense ECM inhibits migration (Salmon et al., 2012). Interestingly, greater mammographic density is correlated with higher incidence of breast cancer (Martin and Boyd, 2008).

Soluble serum constituents can favor contraction and physical remodeling of 3D collagen gel in an integrin-dependent manner using different signaling mechanisms. PDGF can stimulate ECM contraction *via* PI3K and myosin II dependent pathway whereas lysophosphatidic acid can trigger contraction *via* monomeric G-protein in a myosin II independent manner (Rhee and Grinnell, 2006).

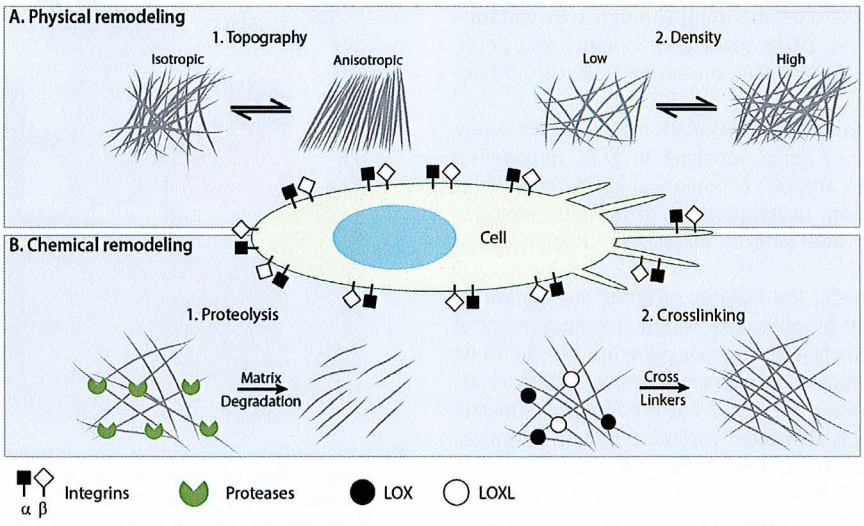

Fig. 2. Diagrammatic representation of ECM remodeling by the cell. Cell-induced ECM remodeling can occur through (A) physical and (B) chemical modifications. Physical modulation can be mediated by ECM topography and density. Additionally, the cell secretes soluble components including proteases and cross-linkers such as LOX and LOXL that degrade and cross-link the matrix respectively, control gene expression in a paracrine manner, and can favor contraction and physical remodeling of ECM in an integrin-dependent manner.

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4.2. Chemical remodeling

Chemical remodeling of the ECM occurs mainly through three processes: matrix degradation, cross-linking, and deposition of new matrix.

MMPs are one of the key enzymes responsible for matrix *degradation* process. MMP activity remains low under normal condition but is stimulated during tissue repair or cancer invasion. MT1-MMP activity is crucial to degrade collagen fibers and form micro-tracks to favor collective migration of cells (Wolf et al., 2007). MT1-MMP deficient mice exhibit severe connective tissue dysfunction due to their inability to remodel the matrix (Holmbeck et al., 1999). Some ECM proteins contain cryptic domains that, once proteolytically cleaved or exposed by mechanical force, can act as a mechanotransducer and regulate cell migration (Lin et al., 2013). For example, collagen I can be degraded by MMP-8 and MMP-9 and produce *N*-acetyl Pro-Gly-Pro fragment, which signals *via* chemokine receptors to regulate the infiltration of neutrophils at inflammation sites (Gaggar et al., 2008). Adamalysins are another family of proteases involved in cleaving membrane adjacent to ectodomains of transmembrane proteins and releasing the entire ectodomain of soluble factors, cytokine, and adhesion molecules (Murphy, 2008). Meprins can degrade collagen IV and fibronectin and are involved in the maturation of collagen I (Broder et al., 2013). In order to preserve tissue integrity, regulation of ECM degradation by endogenous inhibitors of the proteinases is crucial. Tissue inhibitors of metalloproteinases (TIMP) can reversibly inhibit the MMPs and adamalysins but not meprins. The ratio between MMP and TIMP dictates the total proteolytic activity and plays a decisive part in sustaining the structural and functional integrity of the tissue (Khokha et al., 2013).

As opposed to proteolysis, cells can also chemically remodel ECM by *cross-linking* collagen *via* the action of lysyl oxidase (LOX) and LOX-like (LOXLs) enzymes that are often found in greater abundance near metastatic sites (Erler et al., 2006). LOX-induced collagen cross-linking enhances ECM stiffening, integrin clustering, as well as phosphoinositide 3-kinase (PI3K) and focal adhesion kinase (FAK)-mediated signal transduction that trigger invasive phenotypes (Levental et al., 2009). Stiffening of the ECM in turn leads to overexpression of miR-18a and penetration of pro-tumorigenic immune cells (Mouw et al., 2014). ECM cross-linking can also occur non-enzymatically through transglutamination (Mosher and Schad, 1979), glycation (Schnider and Kohn, 1980), and by increasing biglycan and proteoglycan levels (Wiberg et al., 2003).

miRNAs are also involved in ECM regulation and miR-29 family controls the expression of genes involved in ECM remodeling including MMP-9, MMP-2 and LOX (Chou et al., 2013; Sengupta et al., 2008). In breast cancer, overexpression of miR-29b modifies the tumor environment and reduces metastatic invasion (Chou et al., 2013).

Finally, cells can remodel the ECM by *secreting and depositing* its own matrix. Activated fibroblasts secrete increased amount of hyaluronan to facilitate metastatic growth, allowing its level to be used as a prognostic indicator in pancreatic cancer (Kultti et al., 2014). Fibroblast activation protein (FAP) is another matrix remodeling enzyme that is associated with poor patient prognosis and its increased expression has been reported to induce desmoplastic-like aligned fibers (Cohen et al., 2008; Lee et al., 2011). Furthermore, without MMP and FGF synthesis, matrix deposition by fibroblasts has been reported to be necessary for tube formation in the ECM by endothelial cells during angiogenesis (Berthod et al., 2006).

5. Spatiotemporal regulation of cell motility

A clear picture that emerges thus far is that cell motility is strongly dependent on the interactions between the cells and the immediate ECM and is highly dynamic, both spatially and temporally. Various physical, biochemical, and mechanical factors from the matrix, from its own internal signaling and state, and from neighboring cells can influence one another in non-trivial and often dose-dependent ways, and everything feeds back within the interaction cycle (Fig. 3).

5.1. Chemomechanical regulation of cell–ECM interaction

Most of the previously identified physical, biochemical, and mechanical determinants of cell dynamics and migration do not act alone. A growing body of evidence corroborates the spatiotemporally-regulated interplay of these factors.

Cells release mechanical and biochemical signals to the ECM, and corresponding signals from the remodeled matrix feed back to modulate cell behavior. The ECM transmits external forces to cells, and cells reciprocally exert traction on the ECM (Grinnell, 2003). Changes in the substrate or boundary stiffness regulate the expression of proteins associated with cytoskeletal tension and cell–matrix adhesion (Sazonova et al., 2011) as well as the spatial organization of the cytoskeleton (Gupta et al., 2015). These changes further result in alteration of cell contractile forces and orientation (Ghibaudo et al., 2008; Karamichos et al., 2007), and the ability of cells to translocate local collagen fibrils (Miron-Mendoza et al., 2010). The initial ECM stiffness only has a temporary effect on cell behavior, though, as the cells continually remodel and lay down matrix to their surrounding environment (Petersen et al., 2012). Furthermore, cell size, shape, and substrate stiffness can interact in a complex and dynamic fashion to either enhance or antagonize each other's effect on cell behavior (Tee et al., 2011). In effect, cells and matrix dynamically interact to develop tensional homeostasis (Paszek et al., 2005).

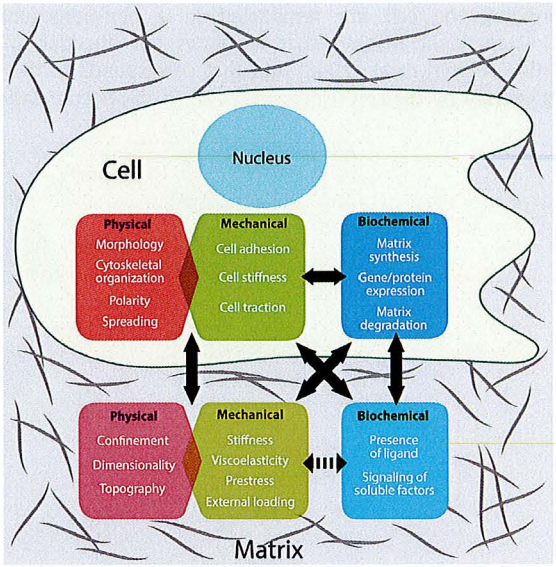

Fig. 3. Schematic illustration of the dynamic interactions between the cell and its surrounding matrix that have been identified in the literature to date. Various physical, mechanical, and biochemical factors and properties of the cell and the matrix interact in a bidirectional manner, as indicated by the two-way arrows, emphasizing the multidisciplinary nature of the mechanobiology of cell migration. The dashed arrow between the physical/mechanical and biochemical factors of the matrix reflects the fact that this interrelation has not been thoroughly explored in the literature.

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Cell–cell interactions have been shown to strongly affect cell morphology in a substrate-stiffness dependent manner: as cell–cell contacts are formed, focal adhesion signaling becomes significantly less sensitive to variations in substrate stiffness (Sazonova et al., 2011). Stiffness-guided cell migration is also affected by cell–cell communications. When cell density was raised such that neighboring cells can transmit forces to each other *via* either direct contact or through the elastic substrate, durotaxis is abrogated and cells can move freely across stiffness gradient (Lo et al., 2000). Experiments of collagen gel contractions indicated that cells within the same matrix can act cooperatively in exerting traction forces (Fernandez and Bausch, 2009). Co-culture of endothelial and breast cancer cells was observed to result in cytoskeletal remodeling and lowered stiffness of the endothelial cells, which promote breakdown of endothelial barrier and facilitate tumor cells extravasation (Mierke, 2011). Furthermore, different cell types can communicate mechanically to elicit matrix remodeling (Swartz et al., 2001). During tumor progression, fibroblasts physically and biochemically remodel the stroma, creating tracks along the ECM that helps the collective cell invasion of themselves and the following cancer cells (Gaggioli et al., 2007; Provenzano et al., 2006; Yamaguchi et al., 2014). In contrast, in individual cancer cell migration, ECM remodeling by mesenchymal cells reduces the speed and directionality of the follower cells, leading to heterogeneity in the migration behavior within the cell population (Sun et al., 2014a).

The cell–matrix tensional homeostasis can be disrupted by mechanical loading. Imposing external tension on 3D polymer matrices can lead to aligned tracks that facilitate cell migration (Raeber et al., 2008). *In vitro* and *in vivo* studies have also shown that external mechanical stimulation alters internal biochemical regulations that are important for cell migration, such as cytokine secretion and matrix remodeling (Glaeser et al., 2010; Kasper et al., 2007; Peters et al., 2015). Indeed, as mechanical stress within the matrix changes, the cell's primary mechanisms to remodel the matrix change as well. The effect of mechanical loading on matrix synthesis has been demonstrated, both at the levels of gene (Karamichos et al., 2007; Popov et al., 2015) and protein expressions (Gupta and Grande-Allen, 2006). As alterations in the ECM architecture can strongly affect its stiffness, these observations suggest that mechanical loading can lead to changes in the force balance between the cell and the ECM as well as in the mechanical properties of the ECM itself, both of which can in turn provoke cell responses in an iterative manner.

5.2. Mechanical responses of ECM arising from cell migration

The mechanical responses of biological materials such as the ECM, with which the cell interacts during cell migration, have been underappreciated and are still not well understood. We will now highlight some of these unique properties.

5.2.1. Nonlinear response

Glass, plastic dishes, and most synthetic gels such as polyacrylamide and polydimethylsiloxane, which are often used as substrates in 2D cell culture, are simple materials in the sense that the mechanical properties are always constant. In stark contrast, fibrous biopolymer networks often exhibit *nonlinear* mechanical properties, which mean that the stiffness of these networks is not constant but changes depending on the extent of deformation (Storm et al., 2005; Wen and Janmey, 2013). Networks of collagen, the main structural component of connective tissues and a popular scaffold for 3D cell culture and tissue engineering, not only stiffen (Motte and Kaufman, 2013), but can also soften with increasing deformation, due to the dynamic nature of fiber cross-linking (Kurniawan et al., 2012b). Fibrin, another important ECM protein that form fibrous networks, also strain-stiffens with multiple regimes that are related to its structural hierarchy: from network-, fiber-, protofibril-, to monomer-scale deformations (Kurniawan et al., 2014; Piechocka et al., 2010, 2015). The cell itself can stiffen (Wang et al., 2002) or soften (Trepat et al., 2007) upon stretch, and this is not surprising as the underlying actin cytoskeleton can also stiffen (Xu et al., 2000) and soften (Chaudhuri et al., 2007; Kirchenbuechler et al., 2014) depending on the extent of filament cross-linking and bundling. This is especially important because highly invasive, metastatic cancer cells are typically softer than normal cells (Guck et al., 2005). This relative softness is attributed to changes in the cell cytoskeleton and can facilitate effective cell locomotion in the presence of obstacle (Cunningham et al., 1992). The changes in the stiffness of these materials when deformed can be very dramatic, up to 100- or even 1000-fold difference in the moduli. The mechanical stress in the cell–matrix system can physiologically arise from combinations of external loading, body movement, blood shear flow, and/or cell traction. The 'effective' stiffness that the cell senses at a particular moment is therefore unclear, but can potentially be very different from the bulk or initial equilibrium properties.

5.2.2. Viscoelasticity

While the role of substrate elasticity has been increasingly recognized, the viscous properties of ECM have received very little attention. This is rather surprising, since most protein scaffolds, hydrogels, and even cells and tissues exhibit significant viscoelasticity and are characterized by time-dependent responses to mechanical stimulations (Levental et al., 2007). Deposition of cell-secreted ECM leads to not only increased matrix stiffness but also altered mechanical relaxation response (Petersen et al., 2012). Substrate viscosity has been reported to enhance correlated epithelial sheet movement (Murrell et al., 2011), suggesting that the cellular mechanosensing machinery is sensitive to substrate flow. A recent study proposed that substrate stress relaxation enables clustering of ECM ligands by the cells (Chaudhuri et al., 2015), which may influence the efficiency of force transmission between cells and the ECM during migration (Coyer et al., 2012).

5.2.3. Reversibility

Another biomechanical aspect that has received little attention is the (ir)reversibility of network deformation. The transient nature of the intermolecular and interfibrillar bonds in biopolymer networks lends its hand in preventing forced rupture and damage propagation, but at the same time makes them prone to plastic (irreversible) structural changes (Bursac et al., 2005; Humphrey et al., 2002; Wolff et al., 2010). By this virtue, the structural and mechanical properties of ECM and cytoskeletal networks adapt to structural deformations and rarely come back to their original states. Consequently, focusing solely on the initial cell and matrix properties during cell dynamics not only limits our understanding, but may in fact result in misleading conclusions.

5.2.4. Spatial heterogeneity

Not only do the ECM stiffness, microstructure, matrix and cellular compositions vary greatly in different organs, tissues, and disease states (Discher et al., 2005; Paszek et al., 2005), but these factors are also inherently inhomogeneous within the matrix (Fridman et al., 2012; Pampaloni et al., 2007). *In vitro*, significant spatial heterogeneity in the local (micrometer-scale) mechanical properties of collagen gels has been quantified (Latinovic et al., 2010; Wong et al., 2014), and its microstructural origins are starting to be unraveled (Jones et al., 2014; Kurniawan et al., 2012a). Moreover, cell-mediated remodeling also contributes in inducing changes in the local stiffness and anisotropy (Wong et al., 2014). These bring up the questions of whether cells sense global

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or local matrix properties, and how far away can a cell feel. Indeed, direct manipulation of the local substrate using microneedle can orient cell polarization and migration direction (Lo et al., 2000). Intriguingly, the fibrillar topography of cytoskeleton and ECM allows local force to be propagated over long distances within (Wang and Suo, 2005) and outside of the cell (Ma et al., 2013). Cell's sensing distance has been estimated from simulation of discrete fiber network (Abhilash et al., 2014) as well as experimental measurement of displacement field within the matrix (Ma et al., 2013; Rudnicki et al., 2013) to be on the order of 10–20 times the cell size. Combined with force-induced fiber realignments, this allows remote mechanical communication between distant cells (Wang et al., 2014).

6. Putting it all together

It is now clear that substrate effect on cell migration cannot be seen just as a one-way response to the cell's microenvironment. Instead, it is a constantly changing two-way communication between the cell and the ECM. Cellular adaptation is therefore part of a mechanical regulating mechanism towards local equilibrium—a state that varies both spatially and temporally during the cell migration process. This presents a challenging problem but at the same time an exciting opportunity for science. How can we measure and monitor this spatiotemporally varying phenomenon? Can we, with this approach, obtain a more complete, holistic physical, biochemical, and biomechanical understanding of cell migration in the context of its native tissue? Can we then exploit the insights to design better treatments for diseases such as fibrosis, cancer metastasis, and cardiovascular disorders, and to develop smart and optimized scaffolds for regenerative tissue engineering?

One way to approach this problem is by developing techniques that can provide spatiotemporal mapping of local forces and mechanical properties. Two promising experimental approaches are micropillar force measurement (MFM) (du Roure et al., 2005b) and traction force microscopy (TFM) (Style et al., 2014a), which provides space- and time-resolved force measurements through quantification and analysis of the deformation of an elastic substrate. Analysis of MFM data is relatively straightforward, as forces can be directly related to the deflection of the micropillars, the stiffness of which is largely determined from geometry. It is possible to create gradient (Sochol et al., 2011) and step changes (Breckenridge et al., 2014) in micropillar stiffness, but the main drawbacks of MFM are that it is only possible for 2D studies and it can be quite sensitive to experimental imperfections (Schoen et al., 2010). TFM was also originally developed for measurements on 2D substrates, but more recently has been successfully advanced for measurements in 3D matrices (Franck et al., 2011; Legant et al., 2013) and even for viscoelastic ECM (Toyjanova et al., 2014). While much effort has been spent on understanding the resultant cell traction forces on the surrounding matrix, quantifying the sources of these forces within the cells is equally important. This proves to be quite an even more challenging inverse problem, however, recent studies have started to tackle this problem by combining experimental TFM measurements with theoretical modeling (Albert and Schwarz, 2014; Soine et al., 2015).

From the matrix's point of view, to cleanly delineate the roles of the different physical and biochemical factors, it is important to be able to control single variables over a large range. In reconstituted ECM such as collagen, for example, matrix stiffness, fiber diameter, fiber density, and pore size can be changed by varying protein concentration, polymerization pH or temperature (Achilli and Mantovani, 2010; Raub et al., 2007; Yang and Kaufman, 2009). While there is a very limited range over which these factors can be altered while keeping the embedded cells viable, several protocols now exist that enable control of each variable independently in the presence of cells (Kurniawan et al., 2015; Mason et al., 2013; Sun et al., 2014b). An alternative and complementary approach is to design synthetic biomaterials with well-controlled and characterized extracellular environments (Lutolf and Hubbell, 2005; Wade and Burdick, 2012). There have also been emerging efforts to design biocompatible synthetic materials with nonlinear mechanical properties resembling those found in natural biopolymer matrices (Jaspers et al., 2014; Kouwer et al., 2013). These approaches open possibilities that are difficult to achieve in natural ECM, especially for temporal control of matrix properties, such as tuning matrix stiffness using light (Wang et al., 2012) or matrix degradability using biophysical and biochemical cues (Kharkar et al., 2013).

From the cell's point of view, a pressing question is: what does the cell feel? One promising approach to answer this question is using microrheology. Microrheology is a technique that allows one to measure local mechanical properties using micron-sized probes (Cicuta and Donald, 2007). It has been used to measure the local viscoelasticity of cells (Wirtz, 2009), actin cytoskeleton (Gardel et al., 2003), fibrin gel (Piechocka et al., 2010), and collagen gel (Latinovic et al., 2010; Shayegan and Forde, 2014), even in the presence of cells (Wong et al., 2014) and in combination with the application of external forces (Kotlarchyk et al., 2011). The clear strength of this technique is the possibility of mapping the local properties of both the cell and the ECM as cell–matrix interactions occur. This allows one to essentially "feel what the cell feels" as remodeling occurs, without having to rely on initial bulk properties. All of these quantitative measurements can be performed simultaneously with dynamic imaging of the cell and ECM during cell migration to provide instructive correlative structure–properties information (Miron-Mendoza et al., 2013).

In the context of fibroblasts, the importance of considering the mechanical interdependence between fibroblasts and the matrix has been recognized, leading to the concept of fibroblast–matrix continuum (Brown, 2013). It is perhaps a good time now to generalize this conceptual framework and start thinking about *cell–matrix continuum* in cell migration.

Conflict of interest statement

The authors declare no conflict of interest.

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