Roles of leader and follower cells in collective cell migration

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ABSTRACT Collective cell migration is a widely observed phenomenon during animal development, tissue repair, and cancer metastasis. Considering its broad involvement in biological processes, it is essential to understand the basics behind the collective movement. Based on the topology of migrating populations, tissue-scale kinetics, called the "leader–follower" model, has been proposed for persistent directional collective movement. Extensive in vivo and in vitro studies reveal the characteristics of leader cells, as well as the special mechanisms leader cells employ for maintaining their positions in collective migration. However, follower cells have attracted increasing attention recently due to their important contributions to collective movement. In this Perspective, the current understanding of the molecular mechanisms behind the "leader–follower" model is reviewed with a special focus on the force transmission and diverse roles of leaders and followers during collective cell movement.

INTRODUCTION

Collective cell migration is a key driver for coordinated multicellular movements that has been widely observed in both physiological and pathological processes, such as blood vessel sprouting, neural crest cell migration, tissue regenerationm and cancer metastasis (Wang et al., 2003; Friedl and Gilmour, 2009; Rorth, 2009; Friedl and Wolf, 2010; Haeger et al., 2015; Scarpa and Mayor, 2016; Barriga et al., 2018; Zhang et al., 2019). The most significant feature of collective migration is directional multicellular movement, which distinguishes it from single cell migration (Shellard and Mayor, 2019). In collective cell migration, a tissue-scale polarization among migrating cells, called "leader–follower" kinetics, has been proposed for persistent directional movement (Figure 1; Omelchenko et al., 2003; Gov, 2007; Poujade et al., 2007; Friedl and Gilmour, 2009; Rorth, 2009, 2012). The "leader–follower" model assumes two distinct cell populations in collective cell migration, that is, leaders and followers, which are categorized by their topology within the migrating cell ensemble (Theveneau and Linker, 2017).

Leader cells are specialized front cells that occupy the leading edge of the collective and assume a "finger-like" structure. In contrast, follower cells, which comprise the majority of the collective, are located in the cell reservoir. Follower cells were long considered to be "passive passengers" that simply moved along with leader cells (Poujade et al., 2007; Rorth, 2012). However, recent studies suggest that in fact follower cells, just like leader cells, become specialized during the polarization process. It is reported that different levels of exposure to extracellular signals stimulate the distinct distributions of adhesion proteins within leader and follower cells (Rorth, 2009, 2012; Khalil and de Rooij, 2019). Specifically, at the leading edge of the collective, leader cells experience asymmetric adherent connections with integrin-based focal adhesions (FA) at their extending fronts (Figure 1A) and cadherin-based adherent junctions (AJ) at their cell–cell connections with follower cells at their trailing edges (Figure 1B; Yamaguchi et al., 2015). However, in the cell reservoir, follower cells experience symmetric AJ adhesions

FIGURE 1: Differentiation and maintenance of leader cells in collective cell migration. Top view of 2D collective sheet migration. Leader cells are front cells in dark blue with polarized centrosome–nucleus axis orientation and distinct "finger-like" protrusion generated from focal adhesions. Follower cells are the major cell population in light blue located in the cell reservoir with random centrosome–nucleus axis orientation and low migratory speed. (A) At the tip of leader cells, large lamellipodia protrusions extend from the cell body and form a "finger-like" morphology. At these sites, strong integrin-based FA connections with ECM activate a downstream PI3K-Rac signaling pathway, which further enhances actomyosin bundle formation and traction force generation. (B) At the rear of the leader cells, transmembrane protein cadherins mediate cell–cell connections with follower cells. At these sites, cadherin-mediated CIL leads to Rho-kinase–dependent myosin light-chain 2 phosphorylation, or Par3/Par6 recruitment at the junctional sites, which result in sprouting inhibition. (C) At the side of leader cells, phosphorylated myosin light chain and F-actin are highly accumulated as thick bundles, which prohibit new protrusion generation from follower cells. (d) Notch1-Dll4 lateral inhibition is reported at the interphase between leader and follower cells, with high Dll4 detected in leader cells, whereas high Notch1 is detected in follower cells. Low cellular stress in leader cells enhances Dll4 mRNA and protein expression, which further determinates the initiation of leader cells and migrating tips. This high Dll4 expression in leader cells enhances the Notch1 expression in follower cells, which in turn inhibits Dll4 expression in these cells. Moreover, high cellular stress also suppresses Dll4 expression in follower cells. (e) Merlin-Rac lateral inhibition is reported at the interphase between leader and follower cells. High contractile forces result in cytoplasmic Merlin through Rac-dependent translocation of Merlin in leader cells, whereas low contractile forces lead to boundary Merlin in follower cells which further inhibit Rac activity and Rac-mediated protrusions in follower cells. (F) At the interphase of lateral membranes between two migrating leader cells, a continuous treadmilling of cadherins is achieved through GSK3-dependent endocytosis processes.

with neighboring cells (Mayor and Carmona-Fontaine, 2010; Khalil and de Rooij, 2019). These differential focal adhesion and adherent protein distributions between leader and follower cells give rise to heterogeneous contractile forces at their cell–cell junctions (Weber, Bjerke, and DeSimone, 2012; Chen *et al.*, 2018; Khalil and de Rooij, 2019), which leads to diverse cellular activities of

PI3K-Rac signaling and Rho GTPases in these two populations (Zegers and Friedl, 2014). As a result, leader and follower cells establish a front-to-rear polarity axis during the movement (Capuana, Boström, and Etienne-Manneville, 2020). Following the polarity establishment, cells within the collective employ several different mechanisms, as described below, that help actively maintain their

polarization and migration (Venhuizen and Zegers, 2017; Alert and Trepat, 2019).

LEADER CELLS: THE LEADER AND THE RULER

Contact inhibition of locomotion

Contact inhibition of locomotion (CIL) refers to the suppression of cell extension at cell edges that contact neighbors. For the leader cells, the asymmetric adhesion results in a biased CIL, generating large protrusions polarized toward the direction of migration (Desai et al., 2013; Ladoux, Mege, and Trepat, 2016; Mayor and Etienne-Manneville, 2016; George, Bullo, and Campàs, 2017). For the follower cells, the symmetric cell–cell adhesions produce essentially uniform CIL that suppresses the formation of large protrusions around their entire perimeter (Mayor and Carmona-Fontaine, 2010; Desai et al., 2013; Ladoux, Mege, and Trepat, 2016).

At the molecular level, CIL involves cadherin-based AJ, Wnt, and Par signaling (Figure 1B). For example, AJ components (Hidalgo-Carcedo et al., 2011), such as cadherins (Desai et al., 2009; Ozaki et al., 2010; Dumortier et al., 2012; Venhuizen and Zegers, 2017) and catenins (Ozaki et al., 2010; Bazellières et al., 2015), are essential for the maintenance of leader cells polarity. During cancer cell collective migration, cadherins at the rear of leader cells interact with Par3/Par6 protein, which recruit RhoE to cell–cell contacts and thereby promote coherent movement (Hidalgo-Carcedo et al., 2011). In the process of neovascularization, cadherin signals lead to Rho-associated protein kinase (ROCK)–dependent myosin light-chain 2 (MLC2) phosphorylation, which promotes actomyosin contractility and thereby inhibits sprouting (Abraham et al., 2009). Moreover, canonical Wnt signaling induces CIL by activating RhoA at the site of cell contact during neural crest migration (Carmona-Fontaine et al., 2008). As a result, CIL enhances leader cell polarization and prohibits follower extension, maintaining the tissue-scale polarity within the migrating collective (Mayor and Carmona-Fontaine, 2010; Haeger et al., 2015).

Physical restriction

Physical restriction is another mechanism that leader cells utilize to prohibit protrusion generation and new leader cell formation from follower cells (Figure 1C; Vedula et al., 2013; Reffay et al., 2014). At the side of the "finger-like" structure in leader cells, phosphorylated myosin light chain and F-actin are highly accumulated as thick bundles (Poujade et al., 2007; Reffay et al., 2014), which restrict new protrusion generation from follower cells. Laser ablation of these bundles releases the restriction, and induces new leader cell formation from the ablated site (Reffay et al., 2014). Moreover, this acto-myosin structure transmits both mechanical and biochemical signaling inside leader cells as well as between leader cells and their extracellular environment (Pandya, Orgaz, and Sanz-Moreno, 2017). The small RhoA GTPase facilitates finger formation (Omelchenko et al., 2003; Reffay et al., 2014; Friedl, Wolf, and Zegers, 2014). RhoA activates ROCK resulting in MLC2 phosphorylation (Pandya, Orgaz, and Sanz-Moreno, 2017) which, in turn, promotes contraction of actin cables and generation of large forces, which serves as a physical restriction prohibiting new leader formation (Pandya, Orgaz, and Sanz-Moreno, 2017).

Lateral inhibition

During the competition with follower cells, leader cells also use several negative feedback loops to achieve lateral inhibition in order to keep their leading position. One is the Notch1-Dll4 loop between leader cells and follower cells (Figure 1D; Riahi et al., 2015). Dll4 (delta-like ligand 4) is a Notch ligand and a molecular signature of leader cells. During collective cell migration, high Notch1 and low Dll4 signals are detected in follower cells. Inhibiting overall Notch signaling increases Dll4-dependent transcription and translation and the number of leader cells (Riahi et al., 2015). However, inhibiting Dll4 suppresses the formation of leader cells (Riahi et al., 2015). In addition, this Notch1-Dll4 feedback loop is mechanosensitive. Pharmacologically or physically reducing the intercellular tension enhances Dll4 expression and increases the number of leader cells (Riahi et al., 2015; Wang et al., 2017), whereas increasing the intercellular tension by cytoskeleton stabilization reduces Dll4 expression and suppresses leader cell formation (Riahi et al., 2015). Therefore, Notch1 and Dll4 regulate leader cell concentration and separate cell dynamics for leaders and followers.

Merlin-Rac also participates in negative feedback in collective movement (Figure 1E; Das et al., 2015). Merlin is a tumor suppressor that acts upstream of the Hippo pathway (Li et al., 2015). Immunofluorescence revealed differential Merlin subcellular distribution in leader and follower cells: Merlin is mainly accumulated in the cytoplasm of leader cells, but restricted to cell junctions in follower cells (Das et al., 2015). This distribution difference is mediated by the contractile pulling force across the cell–cell boundary. In leader cells, high contractile forces result in cytoplasmic Merlin while low contractile forces in follower cells lead to junctional Merlin. Furthermore, the subcellular Merlin distribution is tightly linked to Rac activity in cell movement. Up-regulation of Rac activity using optogenetic tools induces translocation of Merlin from junctions to cytoplasm, whereas RNAi knock-down of Merlin disrupts Rac polarization. Thus, Merlin and Rac form a negative feedback loop to maintain the proper functions of both leader and follower cells in collective cell migration (Zoch and Morrison, 2015).

Adherent junction remodeling

In addition to the mechanisms discussed above, leader cells also take advantage of active AJ remodeling to achieve higher cadherin cycling rate and migration speed (Figure 1F). During collective astrocyte migration in wound healing, a continuous treadmilling of N-cadherin along the lateral sides of adjacent leader cells is observed (Peglion, Llense, and Etienne-Manneville, 2014). In leader cells, a directional recycling of N-cadherin proteins is observed from the leading edge to the lateral cell–cell contacts. Microtubules deliver endocytic vesicles that contain recycling cadherin components as well as catenins from the leading edge to the lateral edge between two leader cells. These AJ components are then moved to the rear of the cell where they are removed from the cell surface by endocytosis, and then delivered to the leading edge again. In follower cells, N-cadherin is less dynamic and the cells form more stable AJ structures. These results suggest a functional role of AJ remodeling in maintaining the polarity, molecular cycling, and migratory speed of leader cells (Hirata, Park, and Sahai, 2014).

FOLLOWER CELLS: UNDERESTIMATED CONTRIBUTORS

To date, it is still incompletely understood how the follower cells actively participate and mechanically contribute to collective cell migration. However, emerging evidence from both in vitro and in vivo studies suggest that these cells play a far more active role than what has been appreciated in the past.

Direct traction force measurement illustrates a large force generated by leader cells and a gradually reduced traction generated by follower cells at the interface between migrating cells and extracellular matrix (ECM; Figure 2; Trepat et al., 2009). However, detailed examination of follower cells revealed that not all followers adhere to the limitations imposed by CIL. That is, cells located in the cell

Control of collective cell migration by leader and follower cells |
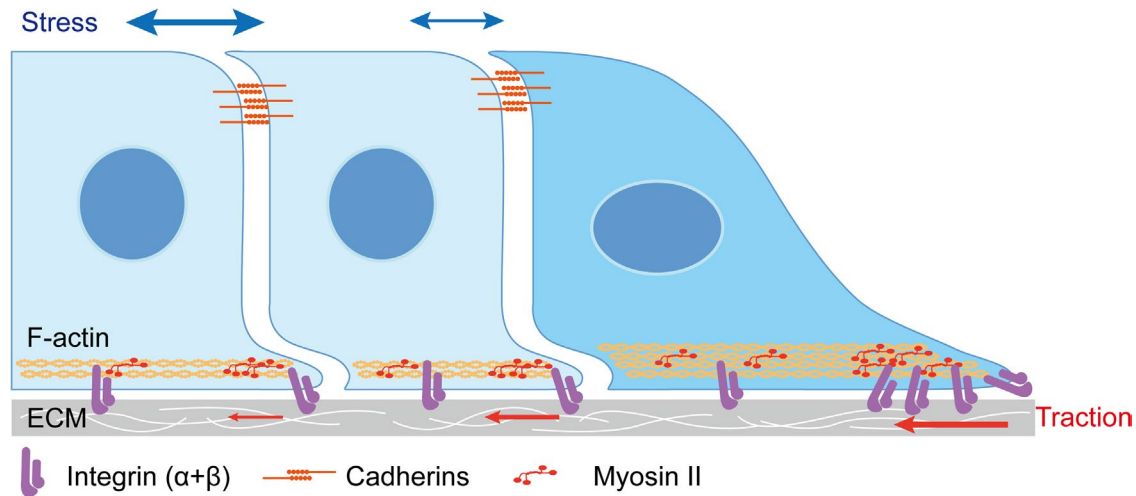
FIGURE 2: Mechanical force distribution in the "leader–follower" model. Lateral view of 2D collective sheet migration. Leader cells in dark blue exhibit asymmetry exposure of adhesions, which includes integrin-based FA at migratory front and cadherin-mediated AJ at the rear with follower cells. Whereas, follower cells in light blue experience symmetry cadherin-mediated AJ with neighboring cells at their apical surface and small FA formation at their basal surface. From the mechanical force perspective, the collective migrating population participates in a global "tug-of-war." The highly accumulated integrins at the migrating tip enable leader cells with large traction forces generated with ECM, and small tractions are recorded in follower cells with their "cryptic" protrusions. The balanced forces to traction are the cellular stress, which is mainly transmitted by the cellular cytoskeleton, and the cell–cell junctions. The stress is built up across the entire migrating tissue, and increases steadily as the distance from the leading edge increases.

reservoir far away from the leading edge can form "cryptic" protrusions on their basal surface (Farooqui and Fenteany, 2005), which are considered as the source of small traction forces generated in followers (Figure 2). These cryptic protrusions mimic the lamellipodia of leader cells, and actively respond to newly formed wounds with directional orientation toward the migrating margin (Menko, Bleaken, and Walker, 2014). Furthermore, cadherin-based AJ proteins, such as WAVE, Arp2/3 (Ozawa *et al.* 2020), phosphorylated myosin II (Menko, Bleaken, and Walker, 2014), and Merlin-Rac loop (Das *et al.*, 2015), participate in the formation of cryptic protrusions. In addition to traction forces, follower cells also mechanically contribute stress force for the collective movement. Newton's third law implies that equal and opposite forces for the basal traction forces in migrating cells accumulate in the form of stress at the AJs of follower cells. Further, this stress, which rises steadily as the distance from the leading edge increases (Figure 2), contributes to collective cell migration (Trepat *et al.*, 2009).

Besides traction and stress generation, follower cells also contribute to the formation of new leader cells (Vishwakarma *et al.*, 2018). Studies using traction force and monolayer stress microscopy revealed that two to six cell layers behind the prospective leader cells exhibited high local cell-matrix traction. This traction was recorded within 30–45 min after wound generation but before leader cell formation. Importantly, this local force generated in follower cells can be transmitted to and pull on the future leaders and help "elect" them to their fate (Vishwakarma *et al.*, 2018). By modifying the force transduction in the cell populations through substrate confinement and pharmacological treatment, it was found that the distance between different local force centers determined the number of newly formed leader cells as well as the physical separating distance between individual leader cells (Vishwakarma *et al.*, 2018). These results suggest that traction forces in follower cells are essential for leader cell formation.

Published results also support that follower cells are more than auxiliary players after the leader–follower polarity is established.

Mathematical modeling suggests that cell-to-cell variation and noisiness of individual cell motion in follower cells increase the overall sensory ability and the collective accuracy of migrating groups (Camley and Rappel, 2017). Moreover, during the collective migration of the zebrafish posterior lateral line primordium, both leaders and followers are required to express sufficient chemokine receptor Cxcr4 in responding to the chemokine Cxc12a, which is essential for coupling and efficient migration (Colak-Champollion *et al.*, 2019). The cadherin expressed in follower cells not only mediates adhesion between leader and follower cells, but also is required for follower cells to pull attractant-blind neighboring cells (Colak-Champollion *et al.*, 2019). Furthermore, the leaders and followers can switch their positions and roles based on their cellular status (Inaki *et al.*, 2012). In the *Drosophila* egg chamber, a cluster of six to eight epithelial cells together with two captured polar cells migrate forward in a tumbling way (Montell, 2003; Bianco *et al.*, 2007). During this process, all epithelial cells in the border cell cluster continuously exchange their spatial position, and keep the cell with highest signal state at the leading front (Inaki *et al.*, 2012). Experiments based on genetic manipulations in *Drosophila* showed that when followers were enhanced with high Rac expression or PDGF/VEGF receptor (PVR) receptor expression, follower cells can swap their position from back to front, become new leader cells, and maintain their position at leading front, controlling the overall cluster migration (Inaki *et al.*, 2012).

In short, the activity and contributions of follower cells are more important than is often recognized: experimental studies show mechanical contributions (Trepat *et al.*, 2009), sensory guidance (Colak-Champollion *et al.*, 2019), and switchable roles (Inaki *et al.*, 2012) for follower cells in collective migration. These results suggest a modified "leader–follower" model for collective cell migration, in which each cell in a collective migrating tissue, whether a leader or a follower, participates in a global "tug-of-war" and contributes to a global tensile stress (Trepat *et al.*, 2009; Ladoux, Mege, and Trepat, 2016; Ladoux and Mège, 2017). We would also argue that as the

majority of the cells within migrating collectives, follower cells are deserving of more attention. Specific avenues of potential research are suggested below.

PERSPECTIVES

Perhaps the most promising approach for learning more about collective cell migration and the relative contributions of leader and follower cells is to take advantage of high spatiotemporal imaging of live cells in 2D and 3D cell culture systems (Liang, Park, and Guan, 2007; Yamada and Sixt, 2019) and in intact animals (Wang *et al.*, 2006; Aman and Piotrowski, 2010; Schumacher, 2019). For example, it was recently found that distinct propagation waves of extracellular signal-related kinase (ERK) were observed in the opposite direction of collective migration (Aoki *et al.*, 2017). This ERK wave tightly links both the leader cells and the follower cells. The initial wave of ERK activation advances in the edge cells (one cell row behind the leaders) where mechanical stretch is generated from polarized leader cells (Hino *et al.*, 2020). Then the ERK activation triggers edge cell contraction, which leads to a pulling force that activates another round of ERK signaling in neighboring cells. As a result, a tissue-scale ERK propagation is generated from leader cells to follower cells (Hino *et al.*, 2020). This stress-polarity coupling between migrating cells may be essential for long-distance transmission of guidance cues and efficient collective migration. Moreover, live cell recordings also reveal that collective cell migration takes place with multiple additional cellular dynamic events (Aman and Piotrowski, 2010; Martin, 2010), such as cell oscillation (Martin, Kaschube, and Wieschaus, 2009; Solon *et al.*, 2009) and active cell intercalation (Bertet, Sulak, and Lecuit, 2004; Caussinus, Colombelli, and Affolter, 2008).

Considering the importance of collective cell migration in development and metastatic invasion, a more comprehensive "leader–follower" model with detailed molecular regulations and diverse contributions from leader cells and follower cells is of great importance for potential strategies for developmental defects, the prevention and treatment for cancers, and advances in tissue engineering.

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