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Review

Collective mechanics of small migrating cell groups

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ABSTRACT

Migration of adhesive cell groups is a fundamental part of wound healing, development and carcinogenesis. Intense research has been conducted on mechanisms of collective migration of adhesive groups of cells. Here we focus on mechanical and mechanistic lessons from small migrating cell groups. We review forces and locomotory dynamics of two- and three-cell clusters, rotation of cell doublets, self-organization of one-dimensional cell trains, nascent efforts to understand three-dimensional collective migration and border cell clusters in Drosophila embryo.

1. Introduction

Large-scale cell migration processes in physiology of health and disease involve movements of groups made of hundreds or thousands of cells. An example of the most researched such phenomenon is neural crest cell migration, which is rather well understood by a combination of experiments [1,2] and modeling [3]. One of the most significant discoveries in this field was the realization that contact inhibition of locomotion (CIL), in which cells repolarize and move away from contact (Fig. 1Ai), is a fundamental mechanism underlying the collective migration [4,5]. Another, equally fundamental mechanism, is contact following of locomotion (CFL), in which two colliding cells of opposite polarity or of the same polarity but different velocities become adhesive and create a synchronously moving doublet (Fig. 1Aii) [6,7].

An important concept that emerged from collective migration research is the notion of leader and follower cells. In the most extreme version of this concept, leader cells at the front edge of the group are actively applying propulsive forces, while remaining cells follow the leader cells passively [8]. There is also the opposite extreme model according to which inner cells in the group polarize in the direction of the external cue and migrate actively, while cells at the group edge do not respond to the directional signal and are pushed along by the inner cells [9]. More complex and nuanced mechanisms of co-active and interdependent motility, i.e. the leaders pulling and the followers pushing [7], or the leader cells pulling faraway followers through deformations of extracellular matrix [10] and the followers pulling on the leaders' rears, and by doing so, facilitating polarization and protrusion formation in leaders [11], gradually replace simpler models. One of the most consequential recent concepts is that of the supracellular collective migration [12,13]: the migratory group behaves as an integrated giant cell, in which cytoskeletal structures are mechanically linked through cell-cell junctions and span across several cells.

The collective cell migration field is extremely active, with not only more than a hundred papers published yearly, but even the number of reviews published so far exceeds hundred. Excellent general reviews of the field [11,14], of physical aspects of the phenomenon [15–17], of physical and computational models of migrating cell groups [17–20] can easily be found. An exceptional and thoroughly referenced review of learning models of collective migration from data has just appeared [21].

Our aim here is to focus mostly on the simplest cases of collective migration – those involving very small cell clusters of just two or three cells together. Many migratory events in development, cancer and wound healing involve small groups of less than ten cells [22]: examples of migrating cell doublets include in vivo tandems of D.discoideum cell pairs [23] and of heart progenitor cell pairs in Ciona [24]; small clusters of cells detach from the primary tumor lesion and migrate within the adjacent extracellular matrix [25]; lastly, the foremost example is much researched border cell cluster migration in Drosophila [26,27]. Aside from the physiological significance of the small migrating groups, it is logical to start understanding basic collective motility mechanisms using lessons from bridging single cells to doublets to triplets to small clusters. Even after narrowing the focus down that much, we cannot cover other important aspects like collision of non-adhesive cells [28] and collective

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direction sensing [29].

In this review, we focus on physical mechanisms and simple mechanistic understanding, and only briefly touch on the vast topic of molecular pathways of collective migration at the end. There is always some danger of building models based on data and lessons from very different cell and tissue types; one always must exercise caution by not extrapolating biological lessons too far, as we no doubt do here. Lastly, even after narrowing the scope, we are not able to discuss and cite a great number of relevant papers, for which we apologize.

2. What happens when two cells collide?

Besides CIL and CFL, two more outcomes have been observed when two cells collide. One is cells sticking together resulting in a non-motile cohesive pair; another is sometimes called contact sliding locomotion (CSL) – the cells just slide past each other and continue to crawl in their respective original directions (Fig. 1C) [30]. These four outcomes occur randomly, with certain probabilities. What are the intercellular interactions underlying these outcomes and determining their probabilities? In Section 9, we review respective molecular pathways; here, we discuss two quantitative studies shedding light on relevant conceptual mechanisms. Authors of [30] model colliding cells as 2D objects with free boundary and reaction-diffusion equations for the protrusive activity in each cell. The interactions in these equations are between an activator, playing the role of Rac and governing local protrusion, and an inhibitor regulating cell persistence. The central hypothesis of the model is to implement two variants of CIL by assuming that additional inhibitor of protrusion is produced when two cells collide: the first variant, contact repolarization, means a cell produces the inhibitor when it is in contact with any part of another cell. The second variant, front repolarization corresponds to inhibitor production only when the cell is in contact with the *front* of another cell. This conceptually simple model can reproduce all four outcomes of the collision by fine-tuning the strengths of adhesion and contact and front repolarization. Intuitively, strong adhesion results a high probability of sticking; CSL is the main outcome if moderate adhesion and dominance of front over contact repolarization are in place; weak contact repolarization and moderate front repolarization lead to CFL; strong contact repolarization and weak adhesion result in CIL.

A similar question was recently addressed in [31] by combining experiments of two cells on two adhesive squares connected by a corridor, and statistical learning theory. Based on the cell trajectory data, a stochastic equation of motion can be learned, which finds that the behavior of the cell pair is determined by an effective distance-dependent force between cells and friction (the latter is friction if cells tend to equalize their velocities with their neighbors, and anti-friction if neighboring cells tends to increase their velocity difference). Simulations of the learned model predict, intuitively, that a combination of (i) a repulsive intercellular force with friction leads to CIL (Fig. 1Ai); (ii) an attraction force with friction leads to CFL (Fig. 1Aii); and (iii) a *weak* attraction force with *anti-friction* leads to CSL (Fig. 1Aiii).

Additional biological insights on the CFL mechanism can be gleaned from [32]: (i) when single cells or small cell clusters moving in opposite directions collide, the 'winning' cells or clusters are characterized by larger lamellipodia that they are able to extend beneath the opposite, 'losing' cell or cluster, demonstrating that coordinated CFL is driven by the repolarization of 'weaker' cells or groups upon collision with cells or groups with stronger protrusive activity. (ii) CFL behavior could stem from cryptic lamellipodia of the follower being stabilized by the rear of the leader through cadherin coupling preventing back-slippage of this follower's lamellipodia and increasing its persistence.

3. From CIL/CFL/CSL of two cells to self-organization of one-dimensional cell trains

One of the main questions of collective motility is how do the interaction rules, such as CIL, CFL and CSL, lead to coherent movement

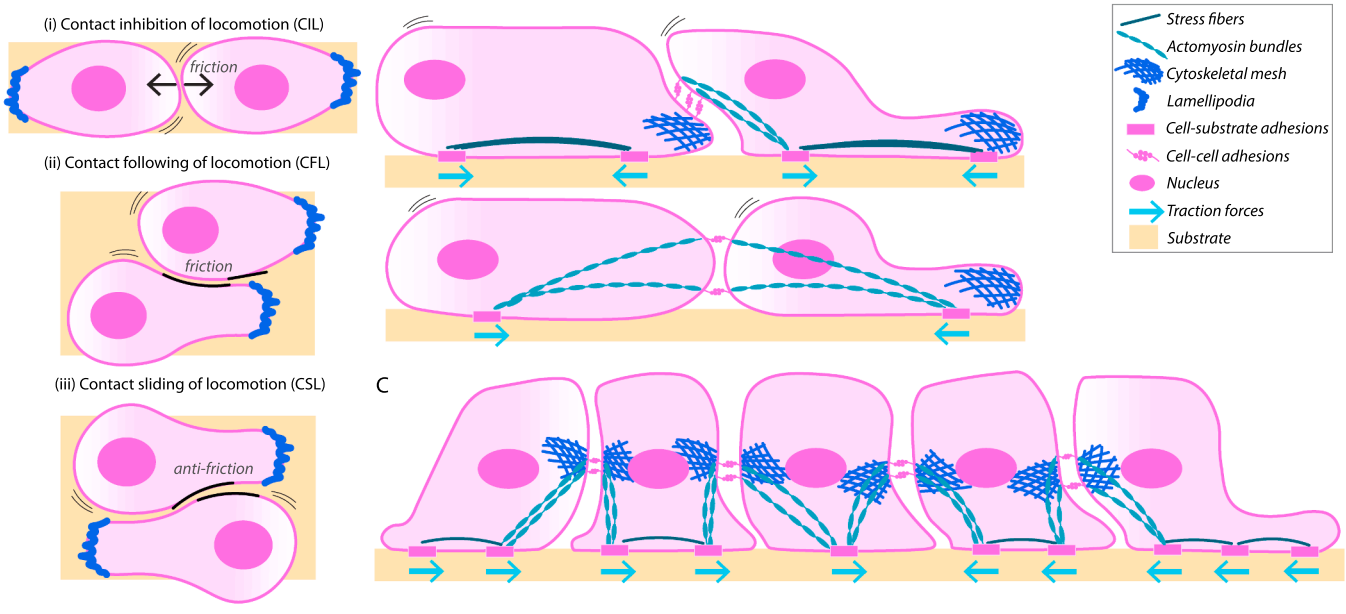

Fig. 1. Organization, rules and forces of small cell cluster motility. A. According to [30], a combination of a repulsive intercellular force with friction (tendency to *equalize* cells' velocities) leads to CIL (top); a combination of an attraction force with friction leads to CFL (middle); a combination of a weak attraction force with anti-friction (tendency to *increase difference of* cells' velocities) leads to CSL (bottom). Arrows show cell velocities. B. Integration of semi-autonomous leader and follower cells into the cohesive motile cluster (top) versus supracellular collective migration (bottom). The main difference between these two modes is the individual traction force dipoles of the cells (top) versus one global dipole (bottom). Arrows illustrate propulsion forces. C. Supracellular force organization in 1D cell clusters according to [12]. Several leading cells apply greater propulsion forces (arrows), while several follower cells generate smaller propulsion forces in the opposite direction. The cells at the edges apply greater forces than the inner cells. The magnitude of the leaders' forces is greater but decreases inward faster compared to the followers' forces. Note that the total vector sum of all forces is zero. Refer to the key in Fig. 1 for notations of schematic cell parts.

of small (less than 5 cells) cell clusters as a unit is largely answered by several studies that examined, both experimentally and with modeling, single-file cell trains on narrow adhesion strips. The earliest of these studies reported persistently moving 1D trains of cells emerging from colliding single cells and asked a natural question: what are the optimal conditions for these trains emergence [33]? This elegant paper proposed the following argument: let a cell colliding with another cell repolarize with probability p and continue to move in the initial direction with probability (1-p). Then, CFL behavior of a cell pair, needed for emergence of two-cell tandem, occurs with probability 2p(1-p) (one of the cells turns around, another does not). This probability is maximized if $p = 0.5$. But what happens when a cell cluster collides with a single cell? The clusters were observed to turn less than single cells, and so to join the cluster, the model predicted that, upon collision, the single cell would have to turn with probability higher than 0.5. Remarkably, measurements confirmed that $p = 0.58$. Thus, probabilistic CIL/CFL rules support the emergence of motile groups if the probabilities are fine-tuned.

Three more advanced models considered the self-organization of individual cells exhibiting pairwise CIL/CFL/CSL behaviors into persistently moving cohesive clusters. The first of them [34], introduced cells as particles moving due to propulsion (traction) force balanced by viscous-like drag. The cells interacted with distance-dependent intercellular forces, attractive over a certain range of intercellular distances (corresponding to cell-cell adhesion), and each cell front tended to repolarize another cell by this intercellular force. Simulations of two-cell collisions showed, expectedly, that when adhesion forces are larger than traction forces, cells remain attached to each other after collision, with traction forces oriented away from each other. In contrast, when traction forces are larger than adhesion forces, cells separated shortly after collision and eventually, moved away from each other. The nontrivial result was that in groups of cells, when cell-cell adhesion is larger than traction, coherent *moving* cell trains exist over timescales that depend on the number of cells in the train. An optimal train size is observed for a given ratio between traction and adhesive forces that maximizes the persistence time of the moving train. Indeed, the persistence time of the train is found to decrease for larger train sizes: when the train is longer than a threshold length, it has greater number of intercellular contacts, and each of these contacts has some rate of repolarization and thus, increasing the chances of breaking up the train. It is less obvious why in the persistence time of short trains increases with its length.

This question was answered by a second model [35], which introduced an exciting physical analogy of cell polarization (left/right) with magnetic spin (up/down) and an energy function of the sum of pairwise cell polarity interactions, which is uncannily like the Hamiltonian describing an idealized magnetic material. Under a certain parameter choices, neighboring cells in the model 'prefer' to be polarized in the same direction. However, the two end cells are always polarized outward, where their free edges point to, and so all cells cannot be polarized equally. The optimal predicted configuration of a short cell train is made of regions of opposite outward polarities, with one boundary between these regions inside the train. This boundary effectively diffuses inside the train, and the train reverses the net direction of locomotion when the boundary passes the middle of the train. The longer the train, the longer the periods between such middle polarity crossovers are, hence longer persistent collective motility of the longer trains. A related and logical observation is that confluent 1D cell trains on circular adhesive strips are extremely persistent and neither stop nor repolarize [32] – indeed, there are no directional intercellular 'conflicts' in such trains – each crawling cell has both a leader and a follower moving in the same direction.

Lastly, the third model [36] brought elements of intracellular dynamics to the problem of cell train self-organization. Namely, this model is based on the popular concept of a positive feedback between single cell velocity and polarity [37]: the faster the cell moves, the more polarity-governing molecules are swept to the cell rear (as a passenger in an accelerating bus would be), enhancing polarization and accelerating the cell. In [36], the authors added two cell-cell interactions to the single cell model [37]: symmetric inhibition of protrusions at the touching cell-cell edges and asymmetric decrease/increase of protrusion at the touching cell edge with a lower/higher speed. Simulations showed that if symmetric interaction is roughly greater than the asymmetric one, cell doublets and triplets exhibit CIL behavior; the opposite case led to CFL effect. Interestingly, there was a narrow region of roughly similar symmetric/asymmetric interactions with bistable, CIL/CFL behavior. The authors found that in experiments the cells were exactly in this bistable region. Finally, application of this model to N cells found, consistently with [34,35], that trains of intermediate length ($N = 14\pm4$) were the most persistent ones: very short trains ($N < 4$) 'trembled' rather than moved, very long trains ($N > 20$) fell apart.

4. Force measurements in cell doublets, triplets and small clusters

Another part of the same question – how cell groups move coherently as a unit – is answered by measurements of traction forces exerted by cohesive cell clusters on adhesive islands of various shapes. Such measurements on cell doublets revealed that each cell in the group generates a total force on the order of hundreds of nN [38,39]. Two simple facts – the total force each cell applies to the substrate is zero, and the force applied by a cell on its neighbor is equal and opposite to the force applied by this neighbor to that cell – allow, after measuring the traction stresses generated by the whole group, to compute the intercellular forces [38–40]. The results of these calculations are pleasingly simple: (i) total intercellular force is roughly tens of percent of the total force; (ii) internal contraction is roughly equally applied to each side of the cell. If that side adheres to the substrate, then certain traction force is applied by the cell to the substrate at that side; If that side adheres to the neighboring cell, then an intracellular force roughly equal in amplitude to the traction force at the opposite side is applied by the cell to the neighboring cell. This principle is starkly apparent in the example of three cells in series [38]: the lateral sides of all three cells attached to the substrate all apply roughly the same inward traction force, and the same is true of two end sides of the edge cells. The interfaces between the adjacent cells in the triplet are tensed by the intercellular forces on the same order of magnitude as each traction force on all other sides. In other words, each cell in the group contracts roughly the same and applies similar force to its surroundings, be it another cell or the environment.

This suggests that the cell-cell junction has a similar mechanical character to focal adhesions, which was also demonstrated [41,42]. The cell-cell junctions were found to have complex structure and dynamics: cadherins [43], myosin [39] and intercellular force [38,39,44] tends to concentrate at the extremity of the junction. Both fine actomyosin mesh and stress fibers transduce in the intracellular forces to the cell-cell boundary, but the mesh is directly connected to the cell-cell junction and therefore, is an effective intercellular force transducer, while the stress fibers mostly apply the forces to the substrate [44] (Fig. 1B). Most importantly, the junctions are mechanosensitive: activation of contractility in one of the cells leads to contractility increase in its neighbors [44], so the intracellular tension spreads to the whole group.

Earlier papers of the collective forces on adhesive islands culminated in a remarkable recent study of small (less than 10), single-file cell clusters on narrow adhesive stripes [13]. Its authors first demonstrated that one active cell, generating propulsion force, is unable to drive locomotion of the whole cluster; several cells must participate in pulling the rest of the cluster for the whole group to move. Second, in the motile group, a small number of leading cells exert a significant propulsion force such that the very leading cell is the strongest, the first follower is weaker, but still pulling, the second follower is weaker than the one before it (Fig. 1C). The propulsion force decreases rapidly from the leading edge of the group inward. Third, nontrivially, several rearmost cells in the cluster apply weak active forces to the substrate that act

against the direction of locomotion; these forces decrease from the rear of the cluster inward (Fig. 1C). Fourth, this nontrivial distribution of bidirectional active forces generates spatially graded, global, asymmetric and centripetal cytoskeletal flow across the motile group, and frictional coupling of this flow with the substrate effectively (but not very efficiently!) propels the group. This global distribution of the forces and flows across the group is deeply analogous to those in a single moving cell [45], reinforcing the concept of the supracellular organization of collective migration.

Perhaps the simplest illustration of the supracellular organization of the motile group comes from the examination of tandem pairs of D. discoideum cells moving during early streaming [46] (see also [7]). 80 % of the time, both cells in these pairs maintain their autonomous single-cell signature: there are large adhesions at the front and rear of both cells, and each cell generates a characteristic traction force dipole, with a strong propulsion at the front and a strong drag at the rear (Fig. 1B). Still, the cells' dynamics are not equal: the rear of the leading cell pulls the front of the trailing cell, dragging the trailer forward. Interestingly, the large 'old' adhesion site at the rear of the leader is periodically inherited by the trailer, so that such adhesion site becomes the 'new' adhesion site at the front of the trailer. Most importantly, the remaining 20 % of the time, only two large adhesions appear in the pair: one at the front of the leader, another at the rear of the trailer (Fig. 1B). In this state, the two neighboring traction force dipoles fused into a single contractile dipole, with all propulsion in the leader and all resistance in the trailer – the pair in this state is supracellular with the leader/trailer cell analogous to the front/rear half of a single motile cell, respectively (Fig. 1B). Intriguingly, in the supracellular state, the pair's velocity slows down.

We are far from full clarity on the supracellular mechanics of even the simplest single-file motile clusters, as they often exhibit both signatures of autonomous cells inside the group, since (i) each inner cell extends cryptic lamellipodia under the cell body in front of it [47], (ii) the migration speed of cell trains of different lengths is similar to the speed of individual cells and does not depend on the number of cells in the train [47], and of supracellular organization, due to the fact that traction forces and cell-substrate adhesions are focused at the front and end, not middle of the train [47]. It is interesting to note that another illuminating study of 1D cell trains [32] found that the traction forces were unevenly distributed, with large forces concentrated at the free edges of the clusters, only at the onset of migration. During steady migration, in contrast, the cluster exhibited features of individual, not supracellular, cell movements: each cell retained its traction force dipoles and moved at single cell speed, and each cell retained the signature Rho-Rac spatial profile of single cells. Additionally, cell–cell junctions were required to initiate collective movement [32] but not maintain it. This study draws attention to an important point: initiating collective motility and maintaining it could rely, in part, on different mechanisms.

5. Side-to-side interactions in migrating cell clusters

In physiology, cells rarely move in a single file. They have neighbors at the sides, not only at the front and rear. Side-to-side interactions in migrating groups are even less studied than front-to-rear coupling. It was observed that adherens junctions undergo a retrograde flow along lateral cell-cell contacts that is supported by the polarized recycling of cadherin from the rear to the front of the cells where it promotes the formation of new junctions [48]. In other words, the lateral adhesions treadmill: they are stationary in the lab coordinate system, as the adherent cells crawl forward; new junctions appear near the fronts and old ones are dissolved at the rear. In principle, these lateral cell-cell contacts could be mechanically neutral, neither helping nor hindering collective migration. However, at least two studies have shown that these contacts slow the cells down: first, cells crawling on wider adhesive stripes in two files were slower than single-file cell train on narrower stripes [47]. Second, cells crawling in channels with the side walls coated with E-cadherins moved slower than in channels with non-adhesive side walls [49].

What might be the origin of the resistive force from the side-to-side cell-cell adhesions? One possibility is the ratcheting mechanism: it is possible that the rearmost intercellular adhesion could disengage only when both cell rears are aligned with this adhesion. Then, if one of the cells is faster than its neighbor, it must pause and wait for the slower neighbor's rear to catch up with the faster rear before the adhesion dissolves and both rears can proceed. This would effectively make the cell pair move with the speed of the slowest cell. Another possibility is that additional cell-substrate adhesions associate with the lateral boundary between the cells, and breaking these adhesions incur an additional cost to the locomotory machine. Not to be forgotten, the side-to-side connections not only slow down the cells, but also play an important role in coupling more leading to more following cells. Lastly, a theoretical model predicts that the lateral connections effectively align cells side-to-side in the group [50] creating an additional order in moving clusters.

There is a fascinating example, although not of a small cell cluster, of combined front-to-rear and side-to-side interactions that are instrumental in collective migration. When fish skin is injured, a cohesive sheet of keratocyte cells spreads from fish scale onto the injury site [51]. Lamellipodia of the cells at the leading edge of the sheet protrude in synch with lamellipodia that are interconnected laterally with each other via actomyosin cables. As the sheet spreads radially out from the scale, its leading edge elongates, and the individual lamellipodia of the leading cells stretch side-to-side. This stretching has limits, and to prevent decoupling of the leading lamellipodia, which would destabilize the leading edge, a follower cell in between and to the rear of two adjacent leader cells becomes connected to the leaders by newly emerging diagonal actomyosin cables. Then, the contractile forces along the cables bring the follower cell forward squeezing it in between the two leaders, adding another leader cell to the stretching edge of the cell sheet [51].

6. Rotation of cell doublets

Not only can cell doublets and small groups of motile cells migrate persistently along straight or meandering paths, but they can also rotate if confined to adhesive patches or to cavities in the extracellular matrix, or even unconfined. Examples of such rotations can be found in physiology and in vitro [52,53]. An important in vivo example of such transient collective rotation involves the positional inversion of just two hair cells first described in neuromasts of the zebrafish lateral line [54,55]. The initial pre-rotation event in this case is the local lateral symmetry break, in which Notch1a breaks the symmetry in the pair of adhesive nascent sibling hair cells by repressing the transcription factor Emx2 in one of them (Fig. 2 A, top). The cells of the pair then move along circular arcs around their geometric center, stopping when one of the cells faces 'West', and another faces 'East'. The sibling hair cells invert positions by moving in ~50 % of pairs inverted, whereas the other half does not exchange positions – it is as if one of the cells is attracted to the 'West', and another – to the 'East', and they rotate if their initial orientations are to the 'wrong' sides, or not – if they face the right sides from the beginning.

One very simple model of two such cells considers them as balls tied by strings to a common center and rotating around the circle [54]. There are attractive potential wells for both cells at the 'West' and 'East' points on the circle, and cells effectively repel each other. This kinematic model describes the cells trajectory statistics well. Another, more sophisticated, model posits that the Notch-Emx2 signaling symmetry breaking event oppositely orients mechanical polarization of the cells, so that one of the cells orients its protrusion to the 'West', another – to the 'East', while their rears adhere to each other and remain at the center [55] (Fig. 2 A, top). Ensuing transient migration of this cell-pair dipole stops when mechanical equilibrium is achieved at the point of the effective torque

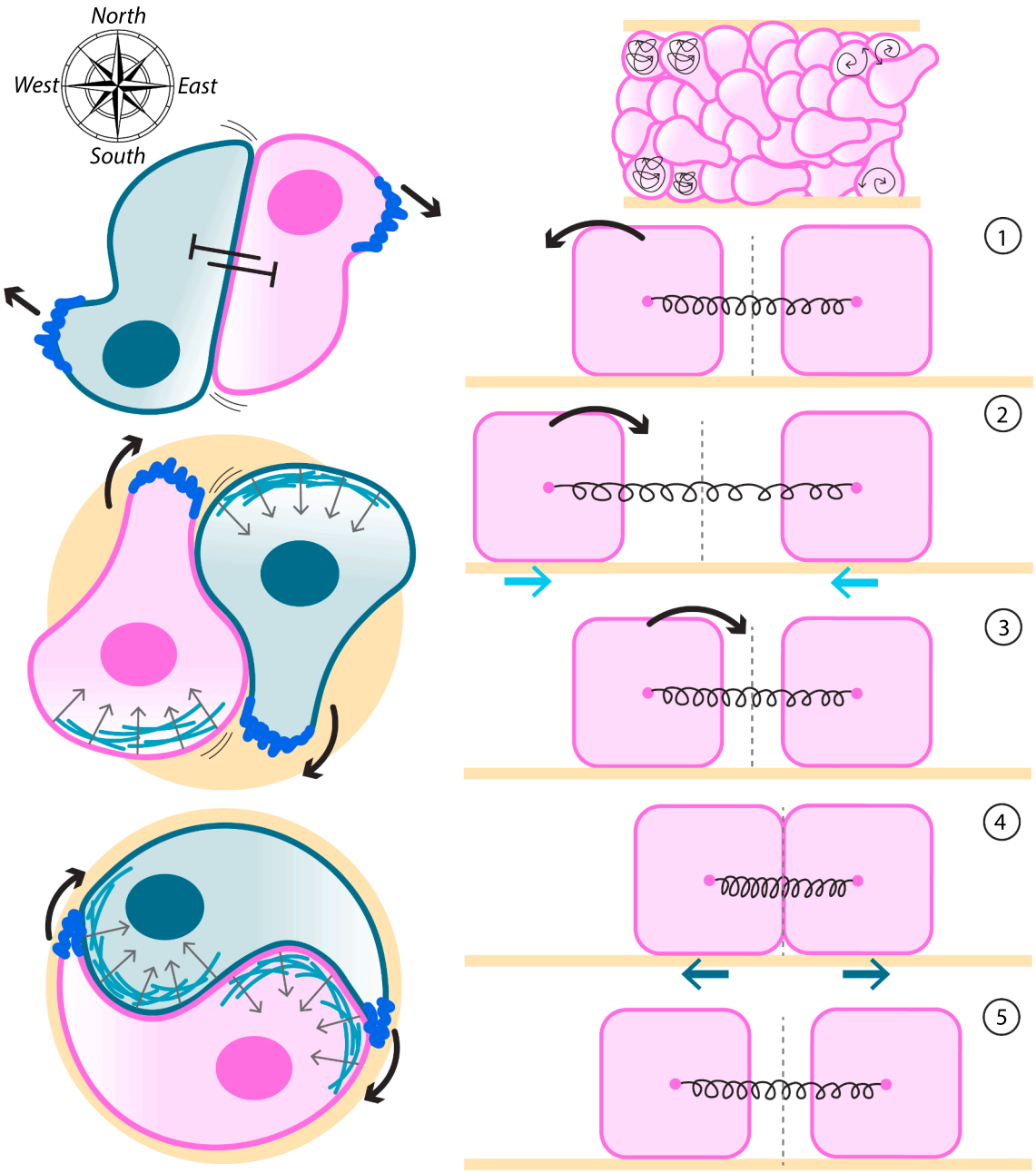

Fig. 2. 2-cell rotations and "jiggling" motility mechanism. A. Top: According to [54], the transient rotation of a cell pair starts with a symmetry breaking event (double-negative signaling) oppositely orienting the mechanical polarization of the cells, so that one of the cells orients its protrusion to the 'West', another – to the 'East', while their rears adhere to each other and remain at the center. Middle: According to [60], the cells generate pointy protrusions from disc-like rears. When a pair of cells like this are cohesive, the pointy ends start going around the convex retracting rears of the partners. Bottom: According to [57], myosin, swept to the rears and outer sides of the rotating cells, generates retractions of convex halves of the cell boundaries forward, perpetuating the very same rotation that keeps myosin biased to the rears and outward. The pointy corners protrude either being pushed by growing actin network or pulled by the retractions of the sister cells. B. Top: Cluster of cancer cells migrating collectively to the right through a channel with low-adhesion walls [75]. Squiggles illustrate more active random "jiggling" of the cells, more active at the rear. Beneath, the schematic locomotory cycle of two cells coupled by effective elastic link (spring) is illustrated. The left cell jumps randomly to the left and right (black arrows). Cyan arrows show forces the cell pair exerts on the walls. These forces are resisted by nonlinear friction when the spring is stretched and not resisted when the spring is compressed. The dashed line shows shifting location of the cell pair's centroid; note the rightward shift of the centroid in the end of the cycle compared to the start. For further details, refer to the text. Refer to the key in Fig. 1 for notations of schematic cell parts.

becoming zero, when the cells pull to the opposite directions from the center along the 'West-East' line. This transient rotation results in segregating the cells to opposite halves of the organ.

A beautiful example of not transient, but persistent rotation of two to four cells in vitro, on a flat 2D adhesive island, was discovered at the turn of the last century [56,57]. The rotating cells developed a sigmoidal common junction ('Yin-Yang shape') (Fig. 2 A, bottom). Interestingly, this rotating pattern was established by endothelial cells, while fibroblasts squeezed together on the adhesive island did not rotate, developing a straight, static interface between the two cells. Recent study demonstrated that this phenomenon is not limited to 2D: two cells trapped in a spherical-like cavity of extracellular matrix rotated around each other in 3D, also exhibiting the Yin-Yang-shaped boundary [58] (Fig. 2 A, bottom). During the rotation, actin was spread along the

cell–cell interface, while myosin and two focal adhesions appeared in the sharp corners of the cell–cell junction. Intriguingly, both in 2D [56] and in 3D [58] the cells rotated with the sharp end forward creating both a challenge and a clear test for models of collective cell rotation (Fig. 2 A, bottom). The puzzle is that usually a single migrating cell has broad protrusive front and tapered rear [59], while it seems that the each cell in the rotating pair has a narrow pointy front and wide rear.

Several such models have been proposed [58,60–62]. The authors of [58] use polar gel theory [63] to reproduce the observed morphodynamics in 3D based on the coupled myosin contraction and kinematics of the rotation. Our interpretation of their results is that myosin is swept to the rear of the locomoting cell and, crucially, in addition, an effective centrifugal effect of the rotation biases myosin to the side of the rotating cell. Then, myosin at the rear and side generates contraction, which retracts the half of the cell boundary forward, perpetuating the very same rotation that keeps myosin biased outward (Fig. 2 A, bottom). The myosin-generated retraction creates the convex half of the boundary; another half of the boundary is retracted by the sister cell, so the protruding part of the boundaries of both cells have pointy corners by default. Active actin-based protrusion seems to play no or minor role in this model (simply conserving cell volumes effectively creates protrusions in the presence of retractions of parts of the boundaries), although Arp2/3 and Rac are necessary for the phenomenon [58]; however, it is possible that Arp2/3 and Rac-induced actin network is used for myosin-powered contraction [64]. There are certain parallels of this cell doublet rotations to pivoting behavior of a single cell [65], in which the main driver of the rotation of a single cell is also the positive feedback between the myosin retracting half of the rear and centrifugal effect of the rotation pushing myosin to the half of the rear boundary.

Another physical model combined the effects of myosin contraction, actin protrusion and membrane tension, to explain the 2D coupled rotation with the Yin-Yang boundary and pointy ends forward, as follows: alone, cells generate pointy protrusions from disc-like rears. Basically, a cell starts looking like a pear with a pointy end forward. When a pair of cells like this are pressed together by the cell-cell adhesion, the pointy ends start going around the convex rears of the partners, generating the observed rotation pattern [61] (Fig. 2 A, middle).

Lastly, a complex computational phase field model similar to [30] (discussed in Section 2) of two highly persistent and strongly adherent cells [62] addressed the question: what is the combination of cell-cell interactions needed to generate rotations? Model simulations demonstrated that the cells rarely rotate if they only interact mechanically. Then, the authors tried combinations of CIL, cell polarity and cell velocity alignment mechanisms, and found that (i) CIL and (ii) alignment of cell polarity to velocity of neighbors do not support robust rotation patterns. The only mechanism that generated consistent rotation was alignment of cell polarity to cell's own velocity: cells deform each other boundaries and then reoriented, because their velocity was no longer outwardly directed. This reorientation ensured that the cells do not become trapped at the boundary, as had occurred with all other mechanisms.

7. Cell pairs and clusters in 3D

With a few exceptions, all collective motility examples discussed in the previous sections are of cell groups locomoting on flat surfaces or adhesive strips. The goal though, is to understand how cells migrate together in the extracellular matrix, a complex 3D environment. One of the simplest such phenomena is cells moving on individual fibers of a low-density matrix with mesh size greater than the characteristic cell size. One recent study elegantly mimicked such phenomenon in vitro by observing motile cells attached to a single fiber [66] (see also [67]). The main result was that two approaching cells rarely repolarized upon contact but rather often migrated past one another. Fiber geometry explained this change of the 2D behavior very intuitively: the colliding cells simply rotated around the fiber, one continuing to move in its initial direction on one side of the fiber, while another cell rotated to the opposite side of the fiber allowing it to continue to move in the opposite direction. Expectedly, when two almost parallel fibers were in proximity to each other, cells often attached to both fibers, which reduced their freedom to reorient. In that case, when two cells collided, the cell pair either started migrating as a group after the collision (CFL), or both cells repolarized (CIL).

In vivo, there are many examples of a small number of adjacent cells squeezed on all sides by other cells [68,69]. Such cell groups look uncannily like foams made of soap bubbles [70]. This is more than a superficial analogy: mechanics of these cells is well approximated by the force balance between the cortex/membrane tension, osmotic/hydrostatic pressure of cytoplasm and line tension of the cells' edges – the same equations that describe the shape of bubbles [68,69]. One of the simplest collectively migrating systems of two such cells is TVC cell pair migrating while squeezed between stiff epidermis and deformable endoderm in Ciona embryo [24]. The rear of these two cells is more contractile [24], and it is possible that the higher contraction of the rear cell generates the higher hydrostatic pressure that pushes the leading cell forward through the tissues, while the same rear contraction retracts the rear of the follower cell, and so this cell pair exhibits the supracellular organization of motility characteristic of larger cell clusters [12]. Another example of the supracellular-shaped cell doublet in 3D is in vitro: rapidly migrating doublets of cancer cells in confined microenvironments have greater actin-based protrusion activity in the leader cell [71].

The principal question about the mechanics of collective cell migration in 3D is what the mode of the group locomotion is. For single cells, most of the mechanical locomotory cycles can be reduced to either mesenchymal [72], or amoeboid [73] motility. Roughly speaking, in a highly adhesive environment, a mesenchymal cell usually extends an adhesive actin network at the front and weakens adhesions at the rear allowing internal contraction to pull the rear forward. On the other hand, in a less adhesive surrounding with confinement, a gradient of the internal contraction is developed generating constant flow of the actomyosin cortex from the middle to the rear [73]. Friction of this flow relative to the surrounding matter propels the cell forward, which may be assisted by the contraction-generated hydrostatic pressure of the cytoplasm pushing the actin-poor front forward [73]. More specialized mechanisms, like an osmotic engine [74], in which the cell harnesses an internal osmotic pressure gradient to suck in water at the front and expel it at the rear, are also possible.

Does a combination of these modes operate to enable the collective migration of the cell clusters? In some systems, this is very likely [75], but there is at least one example suggesting unexpected, fascinating and essentially collective migrating machinery [76] (Fig. 2B). The authors of that study demonstrated that small clusters of cancer cells migrating through low-adhesive narrow channels do not exhibit characteristic multicellular fountain-like flows, with outer cells moving to the rear and cells in the middle moving to the front, which would be expected of collective amoeboid motility [12]. The clusters also neither displayed actin-based protrusions on the channel walls expected of the mesenchymal mode [77], nor slowed down when osmotic engine-promoting mechanisms were inhibited. Instead, after noticing that the cells at the cluster boundaries in touch with the channel walls were engaged in random 'jiggling' (myosin-powered), such that the cells at the rear of the cluster jiggled more than those at the front [76] (Fig. 2B), the authors proposed the motility mechanism based on coupling between random movements, elastic intercellular links and nonlinear cell-wall friction [78]. This mechanism can be understood if one considers the following cartoon (Fig. 2B): let us start with two cells at relaxed distance from each other (the elastic intercellular link is relaxed) and assume that the cell at the right (leader) does not actively moves, while the cell at the left (follower) randomly 'jumps' to both sides with equal probability. If the follower moves to the left (Fig. 2B(1)), the intercellular link stretches

(Fig. 2B(2)). The friction *resisting contractile stress* between the cells (Fig. 2B(2)) is very high, and the cells remain segregated until the follower jumps to the right (Fig. 2B(2)), returning the centroid of the pair to the original position and the link to the relaxed state (Fig. 2B(3)). Then, if the follower jumps to the right (Fig. 2B(3)), the centroid of the pair shifts to the right (Fig. 2B(4)), and the link is compressed. The friction *resisting compressive stress* between the cells (Fig. 2B(4)) is very low, and the link relaxes and pushes the cells apart symmetrically, not shifting the pair's centroid (Fig. 2B(5)). At the end of the cycle, the pair shifts to the right (compare Fig. 2B (1) and (5)). The authors of [76] solved respective stochastic equation of the cell chain and showed that the chain gradually crawls down the gradient of the myosin activity. This example illustrates that very unexpected collective migration mechanisms can be discovered in the future.

8. Border cells cluster

The foremost example of a small cell group migrating in 3D in vivo is a small clusters of ~ 8 cells that migrate during Drosophila oogenesis. This system has been extensively studied and shed light on the basic processes underlying collective cell movements. To organize this cell group, specialized anterior polar cells [79] become the central pair of nonmigratory polar cells, which secrete the cytokine Unpaired activating Jak/STAT signaling and recruit six to eight adjacent border cells. Once specified, the border cells round up, surround the polar cells and form the migratory border cell cluster [80,81], which detaches from the follicular epithelium and migrates in between the nurse cells. The cluster is highly dynamic: at any given time point, one or two cells become leaders, extending and retracting protrusions in between the surrounding nurse cells. The leader's position is randomly acquired and lost, with leader and followers exchanging positions during migration [82]. Interestingly, perturbations that lead to formation of multiple leaders lead to impaired cluster migration [82,83].

The collective polarity of the cell cluster is clear in general: several chemical and mechanical pathways interact to form a coherent actomyosin cable that connects individual cells through cell–cell E-cadherin–mediated junctions [27,84]. One of the Rac1 functional pools at and near this supracellular actomyosin cable form a positive feedback loop with Rho−Myosin-II signaling to govern the integrity of the supracellular cable and maintain mechanical force coupling between border cells for intercellular communication [85]. Another, protrusive Rac1 pool's activity synergizes with Cdc42 signaling to generate actin protrusions in the leader(s) [85]. Additional Rab11-mediated interactions restrict Rac1-dependent protrusive activity to the leader [27] assisted by myosin accumulating at the base of protrusions in the followers where it functions to retract their protrusions [84]. Complex force transmission between border cells through intercellular adhesions and competition of protrusive and contractile networks for molecular resources in each cell are also part of the cluster self-organization [83].

The initial natural hypothesis was that as the leader cell protrudes, it pulls on follower cells dragging them along [27]. However, it is more likely that the tip of the protrusion functions as a sensory organ, and that all border cells actively pull to propel the cluster forward [84]. This view is supported by the elegant experiment with clusters composed of mixtures of wild-type and motility-deficient cells that showed that the more wild-type cells the clusters possess, the faster they migrate [84]. Mechanical details of this collective action are still murky, but two quantitative models coupled with experiments recently shed light on the collective cluster mechanics [86,87].

Dai et al. modeled the border cell cluster as a particle that moves stochastically in an effective potential that incorporates two independent guidance terms: the energy cost for the cluster to squeeze between adjacent nurse cells, and the anteroposterior chemoattractant gradient [87]. The model demonstrated, nontrivially, that these two cues steer border cells into wider crevices of the effective central path along the long axis of the embryo, where more multiple-cell corners are located presenting a lower energy barrier for protrusion of the leader.

Cai et al. posited that each cell of the cluster produces a propulsive force that points along the outward normal to the spherical surface of the cluster and is an increasing function of the local concentration of the chemoattractant, which is highest at the leader and decreases toward the cluster's rear [86]. Integration of all propulsive forces predicted that the net force would scale as the cluster radius in power 3, because the cluster area where pulling force is being exerted increases as radius squared, whereas the difference in the opposing forces between the front and back due to the chemical gradient increases proportionally to the cluster's size, resulting in the cubic power law. Assuming effectively viscous nature of the resistance to the cluster's movement (tissue of nurse cell effectively flowing around the cluster letting it pass), the effective viscous drag scales linearly with the cluster's size. This model predicts that the resulting migration speed of the cluster should scale as the ratio between the force and drag – as the cluster size squared. An elegant experiment with varying cluster sizes confirms this prediction. Above a threshold size, the migration slows down drastically, as super-large clusters get jammed.

9. Mechanochemical complexity of cell-cell communication

There is a bewildering variety of already discovered mechanochemical signaling pathways across the adherens junctions and desmosomes that link neighboring cells in migrating cohesive groups, yet even principal parts of molecular networks of these pathways remain unknown. Many more pathways will no doubt be discovered. Here, we briefly discuss a small fraction of these pathways attempting to focus on common motifs in intercellular communications.

In leader-follower arrangement, a recurrent feedback motif is that local mechanical force of the follower pulling on the rear of the leader is interpreted by mechanosensitive adhesion proteins and regulates small GTPases at the other end of the cell (Fig. 3A). For example, using magnetic beads coated with C-cadherin, Weber et al. demonstrated that pulling forces induce protrusions at the opposite end of the cell in both singlets and doublets [88]. While the mechanism of precisely how this is achieved remains elusive, recruitment of plakoglobin, a catenin family protein, together with knockout perturbations suggests that reorganization of intermediate filaments is needed to ensure formation of lamellipodial protrusions. Similar mechanisms have been implicated in F-actin organization through other members of the catenin family and their local regulation of small GTPases (frequently by slowing turnover rates of GAPs and/or GEFs) [89,90] or microtubule dynamics [91] (Fig. 3B). Despite the evidence that junctional proteins sense the forces acting on them and respond by modifying cytoskeletal structures and/or accessory and motor proteins, how this is done asymmetrically, across a symmetric cell-cell junction, to ensure leader-follower arrangement remains unclear.

Yet, observations from confluent moving epithelial layers may provide key insights into possible mechanisms for establishing this asymmetry. One avenue is through biochemical signaling of different molecular components to polarize the migration machinery at interface, cell, and tissue scales. In Drosophila, follicle cells use Fat2, an atypical cadherin, at the trailing edge of each cell to place both Leukocyte-antigen-related (Lar) and semaphorin ligand (Sema5c) at the leading edge of the cell behind it by slowing down their turnover [92] (Fig. 3C). Both Lar and Sema5c colocalize with the WAVE complex, presumably restricting the protrusive activity to a single leading edge [93,94]. The observation that cadherins (through catenin binding) regulate protrusive structures was also made for *in vitro* systems, where it was shown that adherens junctions are asymmetric; WAVE and Arp2/3 anchor to the 'weak end' of the junction and initiate cryptic lamellipodia there, while myosin-based contractile structures disrupt lamellipodia at the opposite 'strong end' of the junction, generating the quintessential leader-follower contact [95] (Fig. 3D).

In migrating sheets of endothelial cells, the retraction of one cell and

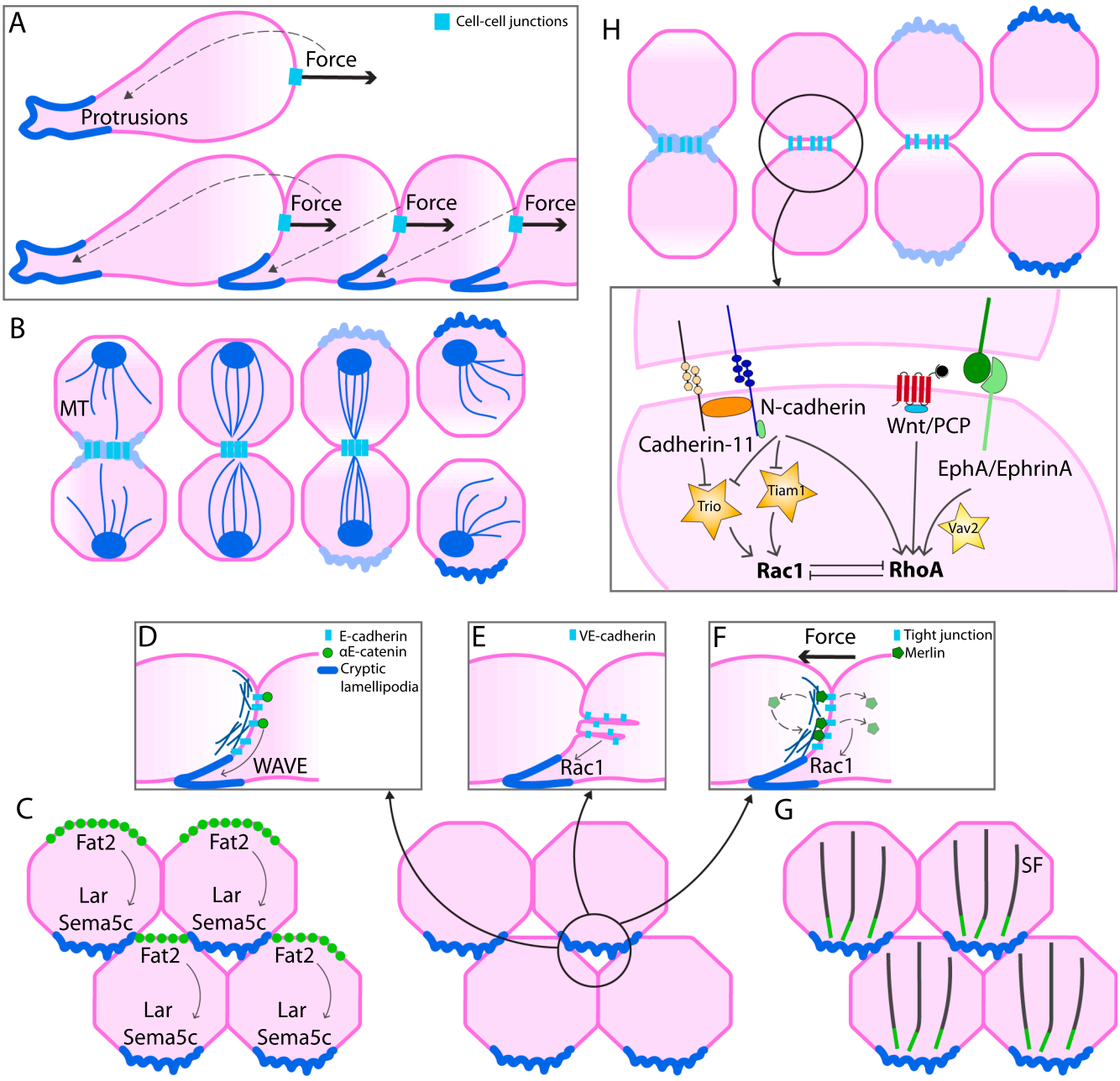

Fig. 3. Molecular mechanisms of collective locomotion. A. According to [87], pulling forces applied to cell-cell junctions on one side of the cell induce protrusions at the opposite end of the cell in both singlets (top), doublets, and cell chains (bottom). B. Microtubule dynamics in each step of CIL. During collisions, cell-cell adhesion proteins are thought to also mediate microtubule turnover rates to allow the cells to re-polarize and migrate in a new direction [90]. C-G. Possible implicated biochemical and mechanical regulations through junctional proteins in confluent tissues. C. Fat2, an atypical cadherin, at the trailing edge of the cell localizes Lar and Sema5c at the leading of the cell, presumably to restrict the WAVE complex at the front [91]. D. Similar mechanism of anchoring the WAVE complex to the 'weak end' of the junction to initiate cryptic lamellipodia there was also observed in vitro [94]. E. In motile endothelial layers, structures, termed `cadherin fingers' [95], were observed to form at the cell-cell junction oriented against the migration direction. Hypothesis is that the difference in curvature of the cadherin fingers ensures asymmetric molecular regulation. F. Asymmetric regulation can also arise from a double negative loop as in [96]. G. According to [97], maintenance of leading/trailing edges can be reinforced through treadmilling of stress fibers. H. Several molecular mechanisms have been identified in mutually inhibiting protrusive activity across the cell-cell junction during CIL (top). The mechanisms can be either biochemical (inset) or mechanical (B). Inset: The biochemical mechanisms, all which have downstream effects on the Rho GTPase (or PI3K) cell polarization pathway, involve cadherins [99–102], the Wnt/PCP non-canonical pathway [103], or Eph/Ephrin receptor-ligand [104,105]. For further details, refer to the text. Refer to the key in Fig. 1 for notations of schematic cell parts.

protrusion of the cell behind it at the common boundary is coupled geometrically through structures, termed 'cadherin fingers' [96] (Fig. 3E). These structures are oriented backwards relative to the direction of movement. Due to their asymmetric structure, it is hypothesized that the difference in (positively or negatively) curved surfaces of follower and leader, respectively, allow for the differential regulation through selective, curvature-dependent, protein binding. Like the Fat2 signaling system proposed in Drosophila follicle cells [92], cadherin fingers are believed to promote protrusive activity, through decrease of actomyosin contractility, in the follower cell.

Rather than physical structures that create junctional asymmetry, a recent study postulates that mechanical stresses are interpreted differently across the cell-cell junction, through a double negative loop Merlin/Rac1 [97]. In the static monolayer, Merlin localizes to the

cell-cell junction. During migration, in response to pulling, Merlin is delocalized from the cell membrane of the trailing cell and removes the repression of Rac1 on the trailing side of the cell-cell junction. On the other side of the junction, the low Rac1 activity, due to the polarized state of the leader, promotes localization of junctional Merlin (Fig. 3F), thus completing the double negative feedback loop. Yet another possibility is that cytoskeletal structures can physically couple the retraction of one cell to the protrusion of the trailing cell (Fig. 3G). In Sherrard et al. [98], treadmilling of stress fibers is maintained throughout an epithelial cell sheet (in Drosophila) through Dishevelled-associated activator of morphogenesis, a component of the Wnt signaling pathway. Perplexing, depletion of the Dishevelled protein increased the migratory speed of the cells, despite slowing down the treadmilling of stress fibers. Presumably this result suggests that stress fibers treadmilling reinforces, rather than establishes, the intercellular signaling to align the cells' front-to-rear axes in the same direction across the tissue [92].

Last, but not least, a conserved group of proteins have been identified to mediate CIL. In two-cell collisions, CIL manifests in four steps: 1) formation of cell-cell adhesion complexes, 2) inhibition of protrusive activity at the site of contact, 3) reformation of protrusive fronts away from the contact, and 4) separation of cells and migration away from each other (Fig. 3H). We discuss the second step, as it involves regulation of the polarization machinery at the cell-cell contact region, but notably, in a symmetric fashion as protrusive activity is inhibited in both cells upon collision. The regulation involves biochemical signaling through junctional proteins either cadherins, Eph/Ephrin receptor-ligand, or the Wnt/PCP non-canonical pathway, reviewed in [99] (inset Fig. 3G). At the intercellular region, protrusive activity is decreased through interactions of cadherins either directly sequestering GEFs of Rac1 (Tiam1 or Trio) [100–102] or indirectly promoting Rho activity [103]. Another mechanism identified was through RhoA recruitment mediated by Wnt/PCP pathway [104]. Yet, a third mechanism is through Eph/Ephrin signaling which either leads to RhoA/ROCK activation via GEF-Vav2 [105,106] or suppression of PI3K, an alternative front-rear signaling pathway [107]. Lastly, the cell-cell adhesions not only regulate small GTPases or other signaling components but also cytoskeletal structures. Namely, a number of studies have focused on the effect of mechanical tension on microtubule organization during CIL [108–110] (Fig. 3B). It remains to be determined if, like in epithelial sheets, this is a reinforcement or a standalone mechanism for intercellular communication.

It is interesting to note that many malignant cells do not display CIL when interacting with other cell types but retain CIL in interactions with each other. For example, prostate cancer cells repel each other, but do not repel from fibroblasts [106]. The proposed explanation is that there are two competing pathways that regulate CIL in the cancer cells: (i) repulsive EphA–RhoA signaling triggered by ephrin-A ligands and (ii) attractive EphB3/EphB4–Cdc42 signaling triggered by ephrin-B2 ligand [106]. The ratio of ephrin-A/ephrin-B2 on a cell will dictate whether the cancer cell colliding with it will display CIL or not. The cancer cells have a high ephrin-A/ephrin-B2 ratio and therefore CIL is induced between pairs of these cells by EphA forward signaling, possibly by activation of RhoA. However, fibroblasts have a high ephrin-B2/ephrin-A ratio which activates EphB3/EphB4–Cdc42 signaling in the cancer cells, stimulating migration and causing defective CIL.

10. Conclusion and outlook

Mechanical and signaling feedbacks and pathways organizing collective cell migration are becoming clearer. Especially, the combined in vitro experiments with small trains of cells on narrow adhesive strips, or on nanofibers, and respective models brought about a consistent set of mechanistic rules for self-organization of cohesively migrating cell clusters. Of note, traditional computational modeling has been recently complemented by very promising attempts to learn cell-cell interaction rules directly from data. Recent measurements and modeling of the traction forces in collective migration provided a much-needed breakthrough in elucidating supracellular effects. Yet, even in the simplest 1D cases, we lack understanding of links between respective mechanical rules and supracellular genetic and biochemical networks enabling these rules and the observed morphogenetic outputs. Even the side-to-side interaction between the adjacent cells are almost completely unclear. The great barrier to this understanding is that intercellular communication unfolds on many different temporal and spatial scales [111]. Another difficulty is the multitude of mechanochemical couplings between adjacent cells and absence of clarity about which of these couplings are redundant vs interdependent, and which are cell type-specific vs more universal. Not to be forgotten, there are subtle similarities and differences between establishment of collective polarity at the onset of migration and maintenance of the group motile state, which only recently started to emerge. One obvious direction of future work will be untangling these multiple mechanochemical interactions and clarifying design principles for asymmetrical regulation in the collective polarity and locomotory machineries.

Beyond the effectively 1D cases, we lack even this limited clarity. What we need is, first, repeating the success of decades of detailed scrutiny of single cells migrating on hard flat surfaces in the case of small cell clusters migrating through engineered 3D deformable scaffolds. Minute understanding of actomyosin-membrane-adhesion networks and of signaling pathways coupled with gene expression patterns in respective modeling systems will be the groundwork for further understanding of the collective migration. Then, the exciting challenge will be to learn the inventory of the migrating modes, which is guaranteed to be more diverse in the cell groups compared to single cells.

Abbreviations

CIL, contact inhibition of locomotion; CFL, contact following of locomotion; CSL, contact sliding locomotion.

CRediT authorship contribution statement

All authors wrote the manuscript.

Declaration of Competing Interest

The authors declare no competing interests

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