© 2019. Published by The Company of Biologists Ltd | Journal of Cell Science (2019) 132, jcs226142. doi:10.1242/jcs.226142

REVIEW

SUBJECT COLLECTION: COLLECTIVE CELL MIGRATION

Supracellular migration – beyond collective cell migration

Adam Shellard and Roberto Mayor*

ABSTRACT

Collective cell migration is a highly complex process in which groups of cells move together. A fundamental question is how cell ensembles can migrate efficiently. In some cases, the group is no more than a collection of individual cells. In others, the group behaves as a supracellular unit, whereby the cell group could be considered as a giant 'supracell', the concept of which was conceived over a century ago. The development of recent tools has provided considerable evidence that cell collectives are highly cooperative, and their migration can better be understood at the tissue level, rather than at the cell level. In this Review, we will define supracellular migration as a type of collective cell migration that operates at a scale higher than the individual cells. We will discuss key concepts of supracellular migration, review recent evidence of collectives exhibiting supracellular features and argue that many seemingly complex collective movements could be better explained by considering the participating cells as supracellular entities.

KEY WORDS: Collective migration, Supracellular, Force transmission, Polarity, Actomyosin cable

Introduction

Collective migration underpins many developmental and pathological processes, including morphogenesis, wound healing and cancer metastasis (Friedl and Gilmour, 2009; Mayor and Etienne-Manneville, 2016). During collective migration, intercellular contacts are maintained as cells move in concert with one another (see Glossary). Whereas individually migrating cells are not physically coupled to other cells, meaning they can move around freely, the cell–cell adhesions present during collective migration necessitates that cells cooperate and coordinate their activities (see Glossary), or else motility is considerably restricted by their adhesions. Consequently, for cell types that can move both as solitary cells and collectively, overall movement is faster and more efficient when the cells are part of a group, because they move in the same direction and with a similar speed; otherwise as individuals, they would be stationary or migrate in different directions (Malet-Engra et al., 2015; Theveneau et al., 2010). These facts suggest that collective migration may not simply be the sum of its constituent parts, that is, cells behaving all as equal individuals, but rather that the complexity of collective motility emerges from physical and chemical communication between cells in the group that affect their behaviour at the level of the tissue.

The requirement of cooperation and coordination in cell groups implies that they can be organised at different levels. On one hand, collectives can be organised at the cellular level, where the function of cell–cell interactions is limited to solely being a means of keeping cells adhered together, with all other aspects of their behaviour unaffected. In this case, cells almost act autonomously, as they would if they were migrating as individuals (Fig. 1A,B), and migration of the group can be entirely understood by understanding the functions of the constituent cells (Fig. 1B).

However, such an understanding of how single cells operate can often only provide a partial explanation of the processes at a higher level of organisation (the collective). Mesoscale phenomena, such as cell jamming or collective gradient sensing, cannot be explained by the activities of the elementary components of the system, such as cells (Good and Trepat, 2018). For example, cells tend to become more jammed as cell density increases; an understanding of the molecular pathways in individual cells is thus unlikely to explain a phenomenon that is at play at the level of the whole tissue (Park et al., 2016). Therefore, collectives can be organised at the tissue level, where the influence of one cell goes beyond its own cell borders, affecting neighbouring and far-away cells. Such a phenomenon of collective movement occurring at a scale greater than that of the individual cells it is comprised of is termed 'supracellular migration' here (Fig. 1C). Thus, we define supracellular migration (see Glossary) as the movement of a cluster of cells at a scale larger than a single cell, whereby migration can be better understood by considering the behaviour of the whole tissue instead of that of each individual cell. Supracellular migration is a type of collective cell migration, but not all collective migrating cells exhibit supracellular migration. In collective cell migration that is not supracellular, all cells contribute equally to the migration; for example, each cell has its own front–rear polarity, forms forward-facing protrusions and contributes forces for movement via actomyosin contractility and focal adhesions (Fig. 1B). In supracellular migration, the entire group can be considered as a single cell; here, the group, and not each individual cell, has a front–rear polarity, the front of the cell group acts like the front of an individual cell (e.g. forms focal adhesions and protrusions), while the rear of the group behaves like the rear of an individual cell (e.g. has high actomyosin contractility), and follower cells recognise that they are not the front of the group, so they do not behave like the 'front' (Fig. 1C).

The idea that a group of cells may behave as a supracellular unit, whereby the cell group could be considered as a giant 'supracell' was first expressed over a century ago. Further accounts referred to wound healing (Ruth, 1911), in which cells appeared to be 'united' to perform functional roles together (Uhlenhuth, 1914). This concept is contradictory to an element of cell theory – the idea that cells are the basic organisational unit of higher order structures like tissues or organisms – and these 'inadequacies' in cell theory (Fig. 2) were also discussed around this time (Baker, 1948; Bourne, 1895; Gerould, 1922; Luyet, 1940; Sedgwick, 1894; Whitman, 1893). These limitations of a cell-centric view to explain mesoscale phenomenon have been reconsidered in recent years owing to advances in methodologies that has allowed scientists not only to understand *in vivo* morphogenesis in great depth, but to also reproduce it *in vitro*. In this Review, we will first identify key

Department of Cell and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK.

*Author for correspondence (r.mayor@ucl.ac.uk)

A.S., 0000-0002-7609-9049; R.M., 0000-0001-9053-9613

Journal of Cell Science (2019) 132, jcs226142. doi:10.1242/jcs.226142

Glossary of key terminology

Collective cell migration: cooperative and coordinated movement of groups of cells; it depends on cell–cell interactions.

Cooperative cell migration: when neighbouring migrating cells influence each other during migration. The influence can be positive (promote migration) or negative (inhibit migration). Cooperative cell migration does not imply coordinated migration and it is therefore different to collective cell migration.

Coordinated cell migration: when the velocity vectors of migration are fully or partially parallel between neighbouring migrating cells. Coordinated migration does not imply cooperative migration, as cells can migrate co-ordinately towards external signals but without cooperation between them. Coordinated cell migration is therefore different to collective cell migration.

Supracellular migration: when the movement of cluster of cells is at a scale larger than that of a single cell and can be explained better by considering the behaviour of the entire tissue rather than that of single cells. Supracellular migration is always coordinated and cooperative, and therefore corresponds to a type of collective cell migration. However, not all types of collective cell migration are supracellular as, in some cases, the movement of individual cells within a group can better explain the movement of the tissue. Supracellular migration often requires the division of function amongst the group; for example, leader and trailing cells play different roles during migration. Full supracellular migration should re-create the movement of the tissue, as individual cells are 'irrelevant' in the context of the tissue motility.

concepts that are associated with supracellular migration, before describing examples that span the range of cellular-based to supracellular-based migration. Finally, we propose how systems that have traditionally been described from a cellular point of view might be better explained based on the supracellular level.

General concepts associated with supracellular migration

Cell collectives can use either highly individualistic or supracellular mechanisms to migrate or combine aspects of both. Thus, supracellular migration is different from collective cell migration.

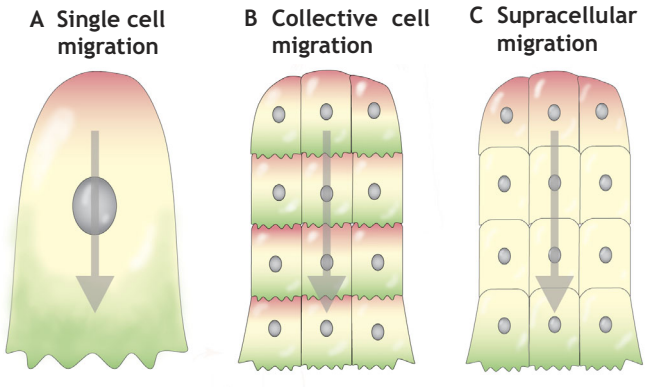

Fig. 1. Polarisation in single cell, collective cell and supracellular migration. (A) Single cell migration. Polarised single cells migrate with a front (green) and rear (red). (B) Collective cell migration. In groups of cells that migrate together, cells are connected through intercellular adhesions, with each cell exhibiting a front (green) and rear (red). Each cell is identical and contributes equally to the movement of the group. Each cell also maintains their (cryptic) protrusions, which contribute to the movement. (C) Supracellular migration. The entire group behaves like a single cell. The cells comprising the group no longer have front–rear polarity and the protrusions between the cells are lost; instead, the entire group exhibits front–rear polarity, with the front of leader cells (green) and the rear of back cells (red) providing the overall polarity.

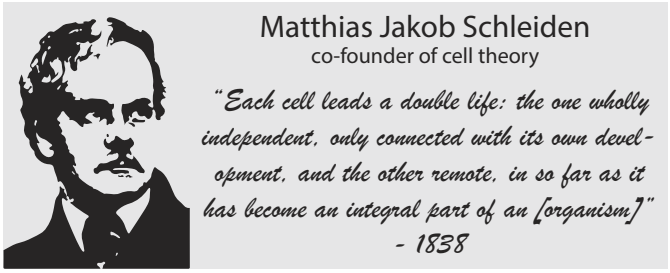

Fig. 2. The 'inadequacies' in cell theory. Cell theory, co-founded by Matthias Schleiden (pictured) and Theodor Schwann.

Below we will highlight a few of the common principles of supracellular migration.

Supracellular polarity

Individually migrating cells acquire front–rear polarity (Fig. 3A, left) (Ridley et al., 2003). For example, Rac-dependent actin polymerisation promotes protrusions at the front, and Rho activates myosin II-dependent contractile forces at the rear. Although during collective migration, the constituent cells of the cohort can consist of polarised and unpolarised cells (Gerhardt et al., 2003; McDonald et al., 2006), the entire cluster acquires a supracellular polarity, and becomes the front and rear of the entire tissue, equivalent to the front and rear of a single cell (Fig. 3A, right) (Mayor and Etienne-Manneville, 2016). This can lead to specialisation in cell functions within the cluster, with some cells being specified as 'leaders' and others as 'followers'. For example, leader cells can guide the migratory group to the correct locations in response to an external cue, instead of relying on each individual cell having to respond to and process the signal. Leaders and followers are often morphologically distinguishable, or otherwise functionally defined (Rørth, 2012); for instance, leaders are more highly polarised in the direction of migration than followers and produce large traction forces. Leaders also typically respond to guidance signals and form protrusions, thereby determining the direction of motion. They influence followers by mechanical coupling, whereas contact between leaders and followers help to polarise leaders, thereby contributing to directional migration. Such supracellular polarity is achieved through different strategies compared to the polarisation of individual cells (Mayor and Etienne-Manneville, 2016). Individuals often respond to an external signal, which is amplified internally by positive feedback, to produce a transient or unstable front–rear polarity (Ridley et al., 2003), whereas collective polarisation is amplified and stabilised through cell–cell adhesions. Leaders can be induced by follower cells either mechanically, through the physical forces produced by follower–leader cell–cell contact (Ladoux et al., 2016; Vishwakarma et al., 2018), or chemically (Carmona-Fontaine et al., 2008; Labernadie et al., 2017), for example, through contact inhibition of locomotion (CIL), whereby signalling at cell–cell contacts inhibits local protrusion formation, thereby stabilising protrusions in leader cells. Furthermore, although intrinsic factors can contribute to the selection of leader cells (Gaggioli et al., 2007; Hellström et al., 2007; Siekmann and Lawson, 2007), leaders are often overtaken and replaced by follower cells (Arima et al., 2011; Bianco et al., 2007; Jakobsson et al., 2010; Prasad and Montell, 2007), suggesting that there is some plasticity in leader fate.

Supracellular polarity is also enhanced by external guidance cues, which promote migratory signalling pathways at the leading edge (Theveneau et al., 2010; Wan et al., 2013). This strategy is used by

Journal of Cell Science (2019) 132, jcs226142. doi:10.1242/jcs.226142

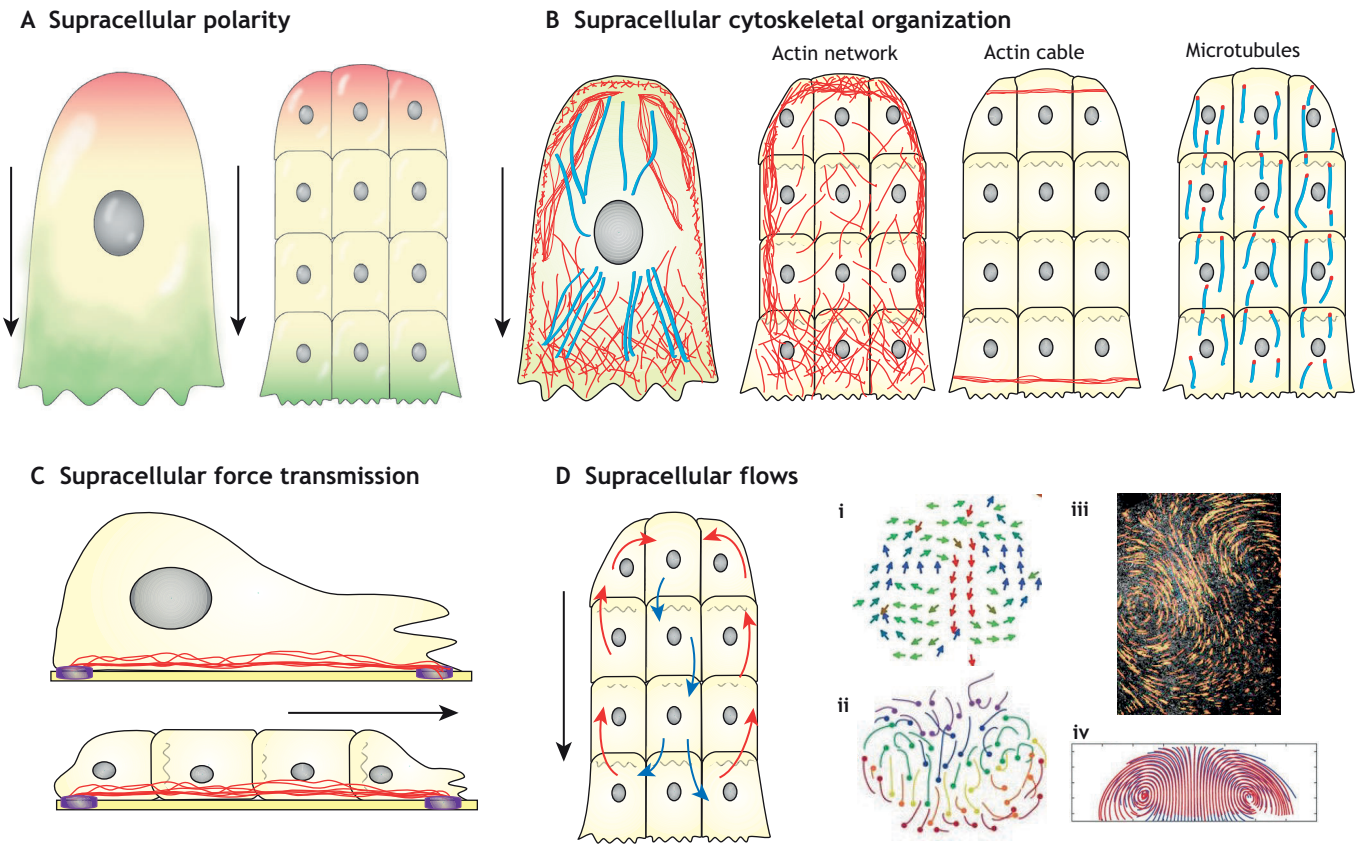

Fig. 3. Principles of supracellularity compared to single cells. (A) Polarisation. Single cells (left) are highly polarised along the front–rear axis (front in green, the rear in pink). The individual cells that comprise cell collectives (right) can be polarised or not, but the tissue as a whole needs to be polarised for directed migration (arrow). This often leads to some cells becoming leaders (green), and other followers, which take on distinct roles. (B) Cytoskeletal organisation. A single cell (left) exhibits a network of cytoskeletal elements, including actin cables or stress fibres (thick red lines), a network of actin filaments (red mesh) and microtubules (blue). Cells within supracellular entities show a highly organised supracellular cytoskeleton (three schemes on the right). This can include an actin meshwork that is associated with the edge of the entire group (red mesh), a bundle of supracellular actin fibres (thick red lines), such as those found at the wound edge or at the rear in neural crest cell cohorts, or an alignment of microtubules according to their polarity (blue, with tip ends red), as has been observed in follicular cells in *Drosophila*. (C) Force transmission. In single cells (top), stress fibres (red mesh) are the mechanical link between adhesion-forming complexes (purple) at the front and mature complexes at the rear. In supracellular collectives (bottom), contact inhibition of locomotion (CIL) can inhibit the formation of focal adhesions (purple) near cell–cell contacts, and forces are transmitted between cells through intercellular adhesions. (D) Supracellular flows. With a supracellular group, cells move forward through the middle of the group (blue arrows, left panel) and cycle back around the sides (red arrows, left panel). This is an emergent behaviour in the motility of supracellularly migrating groups and is often driven by anisotropic forces. As a consequence, the entire group moves forward (black arrow). Shown in the four panels on the right are examples of supracellular flows: (i) collective cranial neural crest cell chemotaxis in *Xenopus* and zebrafish. Arrows indicate direction of movement, as do colours – red is forward, blue is rearward. Reproduced from Shellard et al. (2018). Reprinted with permission from AAAS. (ii) Mammalian hair follicle movement during polarisation (circles at the end of lines indicates the direction of movement, and colours are arbitrary for the initial cell position). Reprinted by permission from Springer Nature, Nature Cell Biology (Cetera et al., 2018). (iii) Epiblast trajectories during primitive streak development (the green dot at the end of the track is the 'front' in the direction of migration). Reprinted by permission from Springer Nature, Nature Cell Biology (Rozbicki et al., 2015). (iv) *Drosophila* ventral furrow invagination (membrane movement is red, cytoplasmic movement is blue). Reprinted by permission from Springer Nature, Nature (He et al., 2014). Note that in all panels, the direction of movement (front) is towards the bottom.

cell collectives that self-generate a chemokine gradient along the group, such as in the zebrafish lateral line primordium. The lateral line primordium is an embryonic structure that is the origin of the sensory organs located at the surface of aquatic animals. It migrates as a cluster of cells, and follower, but not leader, cells endocytose the chemoattractant stromal cell-derived factor 1 (SDF1, also known as CXCL12), thereby allowing the cell group to create a gradient from an initial uniform external SDF1 (Dona et al., 2013; Valentin et al., 2007; Venkiteswaran et al., 2013).

Supracellular cytoskeletal organisation

One of the primary manifestations of supracellular polarity is a tissue-scale organisation of the actin and microtubule cytoskeletons (Fig. 3B) (Röper, 2013). Multiple cells can be mechanically and functionally linked beyond their cell–cell contacts through connections between their intracellular cytoskeletal networks (Sanchez-Corrales and Röper, 2018). The supracellular order and alignment of cytoskeletal structures, such as actomyosin cables or microtubules, contribute to supracellular polarity, long-range force transmission and cell behaviour, thereby playing a vital role in the coordination of cells and the group as a whole.

Cells can be connected by thick bundles of actin fibres, called actin cables (Fig. 3B), which have been observed during collective migration of many developmental processes (Behrndt et al., 2012; Brugues et al., 2014; Franke et al., 2005; Jacinto et al., 2000; Simske and Hardin, 2001; Solon et al., 2009), and in the collective invasion of various cell populations, such as cancer cells, epithelial cell lines and neural crest cells (Hidalgo-Carcedo et al., 2011; Reffay et al., 2014;

Shellard et al., 2018). In most cases, cells exhibit both a supracellular cable and cellular protrusions at their leading edge (Brugues et al., 2014; Reffay et al., 2014; Wood et al., 2002), indicating that cells undergoing collective migration can combine both cellular and supracellular methods to move. Cells can also be connected through apical adherens junctions by the presence of a dense actin meshwork of interlinking filaments at the junctions that associates with the cell cortex (Fig. 3B) (Coravos et al., 2017). In addition, pulsatile behaviour of the apical actomyosin network drives a large number of morphogenetic events, including ventral furrow invagination, germband extension, and in the shaping of the developing *Drosophila melanogaster* oocyte by the surrounding follicular epithelium (Coravos et al., 2017; He et al., 2010; Martin et al., 2010; Rauzi et al., 2010). There is also evidence of supracellular organisation of the microtubule network (Fig. 3B), which align by their tip ends during oogenesis (Jacques et al., 2013; Verger et al., 2018; Viktorinova and Dahmann, 2013). However, microtubule supracellularity has been less studied than actin supracellularity.

Supracellular force transmission

The coordination of forces is essential for directed migration. In single cells, traction and contraction forces drive migration because the intracellular cytoskeleton is intimately linked to focal adhesions and motor proteins (Ridley et al., 2003) (Fig. 3C, top). In collectives, cells also produce traction forces on the underlying substrate and myosin II-dependent contractile forces, which contribute to movement (Friedl et al., 2014). To achieve efficient migration, cell groups propagate these forces over long distances to other cells in the cluster through strong cell–cell junctions and by using their established supracellular cytoskeletal network, as discussed above (Fig. 3C, bottom) (Labernadie et al., 2017; Sunyer et al., 2016; Tambe et al., 2011; Trepat et al., 2009; van Helvert et al., 2018; Vedula et al., 2014). Supracellular force transmission is essential for collective migration in response to chemical (Shellard et al., 2018) and mechanical signals (Sunyer et al., 2016; Tambe et al., 2011). Moreover, coordination of cell behaviour through transmission of stresses can be achieved not only physically, but also chemically, via the recruitment of proteins, such as merlin and α-catenin family proteins, to cell–cell junctions; this then induces a mechanoresponse in the interacting cells (Das et al., 2015; Weber et al., 2011; Yao et al., 2014; Yonemura et al., 2010). Transmitted forces can also affect downstream regulators of Rho GTPases, which control intracellular signalling and help convert mechanical forces into a tissue-scale polarisation (Barry et al., 2015; Das et al., 2015; Reffay et al., 2014; Shewan et al., 2005; Wang et al., 2018; Weber et al., 2012). Contractile stresses that are propagated through actin cables or actin meshworks also promote supracellular polarity and overall cohesion (Hegerfeldt et al., 2002). Thus, supracellular forces actively promote collective migration by enhancing polarity, and by affecting the forces exerted by and on moving cells.

Supracellular flows

During collective, but non-supracellular migration, cell movement is usually linear with little exchange among neighbour cells. By contrast, in supracellular migration, cells tend to exhibit large-scale cell flows. A common flow pattern is the forward movement of central cells, which, once they reach the front of the cluster, engage in backward movement through the cluster periphery, generating stereotypical vortices (Fig. 3D, left). The appearance of these vortices occurs because cells exchange places with their neighbours in precise patterns. Such large-scale rotational movements are common (Fig. 3D, right panels) and occur during the collective migration of epiblast cells during primitive streak formation (Cui et al., 2005; Rozbicki et al., 2015; Voiculescu et al., 2007), collective neural crest cell chemotaxis (Shellard et al., 2018), mammalian hair follicle morphogenesis (Cetera et al., 2018), vertebrate tail bud extension (Lawton et al., 2013) and neuroectoderm epiboly (Smutny et al., 2017), as well as in convergent extension (Bertet et al., 2004; Blankenship et al., 2006; Irvine and Wieschaus, 1994). Long-range supracellular anisotropic tensile forces can provide the driving force for such mass cell flows (Mongera et al., 2018; Shellard et al., 2018). Additionally, such flows can emerge from the activity of the individual constituent components. These cell flows are reminiscent of the Marangoni flows that are observed in liquids, which are generated by surface tension gradient flows (Kim et al., 2017), and are observed at the level of the collective. Therefore, supracellular flows can be better explained as a mesoscale phenomenon than one that is based on the activities of individual particles or cells.

Altogether, we can conclude that cell–cell contacts not only maintain the integrity of the group, but also coordinate its constituent members, thereby contributing to supracellular polarity, cytoskeletal organisation, as well as force generation and transmission.

Different levels of supracellular migration

Supracellular migration can be described as a continuum from none to full supracellular behaviour, depending on to what extent the migration uses features of individualistic and supracellular motility. To better illustrate this continuity, below we discuss examples of cell migration that exist along this spectrum.

Single-cell migration

Individually migrating cells do not move in a collective or supracellular manner. However, in some cases, single cells can migrate co-ordinately, when, for example, a group of cells respond to external signals together. For example, groups of single cells moving in response to a chemoattractant might appear as collective migration, but if the cells move independently without any cooperativity between them, their migration cannot be considered as collective. In the absence of external signals, individually migrating cells tend to be randomly polarised, which makes their migration uncoordinated (Ridley et al., 2003). For instance, cells can go around in circles, or constantly change the direction of their movement (Fig. 4A). More persistent migration is exhibited by cells that respond to external signals, such as chemokines or growth factors, which amplify and stabilise front–rear polarity in each of the cells (Fig. 4B). For example, primordial germ cells (PGCs), the progenitors of gametes, migrate in a directed fashion to the presumptive gonad in *Drosophila* and zebrafish as a mass of individually moving cells because they respond to attractive and repulsive cues, including SDF1 (Doitsidou et al., 2002), which directs the formation of forward-facing blebs (Blaser et al., 2006). However, these coordinated movements cannot be considered as collective migration.

Collective migration with low supracellularity

Cells can exhibit collective migration (i.e. coordinated and cooperative migration) with low supracellularity, when the mechanism underlying their movement depends mainly on the activities of individual cells, such as when each cell is producing its own polarised protrusions and generating its own force for migration. When cells are connected, migration is more efficient. Coordination is high because cells are physically coupled, which means they must move in the same direction. However, collective

Journal of Cell Science (2019) 132, jcs226142. doi:10.1242/jcs.226142

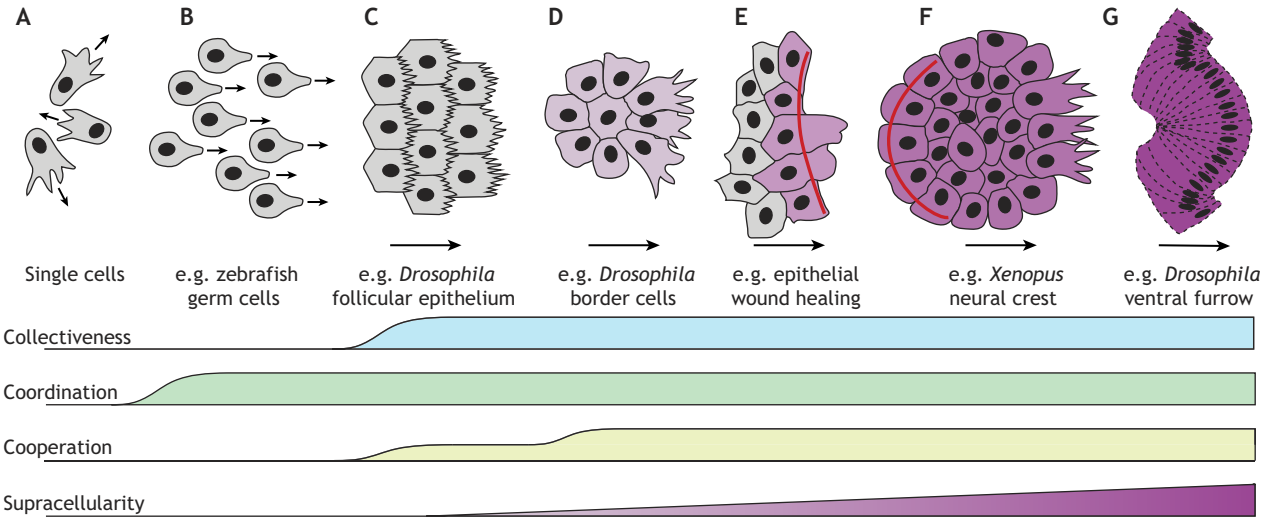

Fig. 4. Varying degrees of supracellularity in cell migration. (A) Single cells migrating in random directions (black arrows) in the absence of external signals lack coordinated movement. They move as individuals; this means they are not collective and do not cooperate with each other, nor have any supracellular features. (B) Mass movements of individually migrating cells, such as zebrafish primordial germ cells illustrated here, are coordinated by their response to SDF1 (indicated by the black arrows). However, they do not move as a collective, cooperate with each other, nor show supracellular features. (C) Collectively migrating cell populations such as the follicular epithelium begin to show cooperation and supracellular features, such as microtubule alignment. (D,E) Moderate supracellular features are more evident in migrating groups that have a free edge, such as *Drosophila* border cells (D), or cells involved in wound healing (E). Here, supracellular structures, such as an actomyosin cable (shown in red) and supracellular forces are at play. (F) High levels of supracellularity are exhibited by mesenchymal groups such as the neural crest; here, supracellular flow is a consequence of supracellular forces. (G) Full supracellularity has been demonstrated in the *Drosophila* ventral furrow, whose collective behaviour can be reproduced in acellular embryos (represented by dashed lines), thereby demonstrating that tissue movement is a not a consequence of individual cell movement.

migration does not necessarily require high levels of cooperation. In some cases, the cell–cell contact functions solely as an adhesion mechanism, with little effect on the migration of neighbour cells.

An example of such a collective migration with low supracellularity is the migration of the *Drosophila* follicular epithelium, a single cell layer encapsulating the egg chamber whose motility causes the egg chamber to rotate and elongate (Fig. 4C). Every cell contributes equally toward collective movement; each cell produces a forward-facing protrusion and retains its position relative to its neighbours (Barlan et al., 2017). Also, each cell has stress fibres anchored to integrins, forms focal adhesions and produces the forces required for its movement (Bateman et al., 2001; Gutzeit, 1990); this means that each cell is a replicate of every other. There is cooperativity between adjacent cells; protrusions are formed because of the interaction between the rear of one cell and the front of another (Barlan et al., 2017; Stevenson et al., 2019; Viktorinova et al., 2009) to polarise the individual cells. Therefore, an understanding of collective migration of the follicular epithelium can be obtained at the level of individual cells. Although this migration is mostly individualistic, there is a small degree of supracellularity: the planar polarisation of microtubules contributes to directing rotation of the egg chamber by helping to establish supracellular polarity (Chen et al., 2016; Viktorinova and Dahmann, 2013), perhaps by delivering proteins, such as the atypical cadherin Fat2 (also known as Kugelei), which promotes cell protrusions in a non-cell-autonomous manner, to the rear of cells. Also, actin filaments are all globally aligned across the tissue (Gutzeit, 1990), although the functional relevance of this, beyond the orientation of traction forces, remains unclear.

Supracellular migration

This category exhibit features of both supracellular and individualistic motility, and we find collectively migrating cells, in which the entire group is polarised, the cytoskeleton is supracellularly organised, or the forces are generated in a supracellular fashion. However, at the same time, some cells within the group behave more like individual cells. Many migrating epithelia that have a free edge fall in this category. For instance, border cells of the *Drosophila* ovary, a group of somatic cells required for the formation of the micropyle (the sperm entry point), form external-facing Rac1- and actin-dependent protrusions when they undergo chemotaxis in response to platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), and cells move almost linearly (Fig. 4D) (Bianco et al., 2007; Cai et al., 2014; Fernandez-Espartero et al., 2013; Prasad and Montell, 2007; Wang et al., 2010). At the same time, there is an overall front–rear polarisation of the cell cluster (supracellular polarisation) owing to the polarised activity of PDGF/VEGF-related receptor (PVR), which further enhances Rac1 activity at the front of the cluster, with one or two cells leading the others (Duchek et al., 2001; Poukkula et al., 2011). However, the effect of the non-leader cells on the collective migration of border cells has not been studied in detail, and therefore it is not clear whether the entire cluster moves as a single unit (i.e. supracellularly), with leader and trailing cells having different functions, or whether leader cells just pull the trailing cells. The latter would correspond to a more cellular type of migration. Although cells move mostly linearly during border cell migration and myosin has no supracellular organisation (Combedazou et al., 2017; Edwards and Kiehart, 1996), some evidence suggests that, in the latter stages of border cell migration, cells exchange positions more often (Duchek et al., 2001; Poukkula et al., 2011), and actomyosin is organised peripherally around the cluster (Combedazou et al., 2017). These changes are reminiscent of a switch from individual cell-driven collective migration to supracellular migration.

Similarly, aspects of both individual and supracellular motility exist in migratory cell sheets. The constituent cells of monolayers invading a free space exhibit front–rear polarisation; each cell

produces lamellipodial protrusions and generates traction forces on the underlying substrate (du Roure et al., 2005; Trepat et al., 2009), in a manner similar to individually migrating cells. For follower cells, that is, those not at the migration front, such traction might arise from so-called 'cryptic' lamellipodia (Farooqui and Fenteany, 2005), although it is still debated to what extent cryptic lamellipodia can generate force to propel collective movement (Kim et al., 2013; Trepat et al., 2009). Traction forces are balanced by tensile forces at cell–cell junctions, with forces being transmitted over long distances across multiple cells within moving sheets (Bazellieres et al., 2015; Trepat et al., 2009); this leads to long-ranged gradients of tension that can guide the direction into which epithelial and endothelial monolayers move (Tambe et al., 2011). Supracellular transmission of contractile forces also drives collective cell durotaxis, the movement of cells up a rigidity gradient; here, a gradient of intercellular tension is generated from the imbalance of traction forces at the edges of the collective, with one edge sensing a stiffer substrate than the other, which leads to directional movement of the group (Sunyer et al., 2016).

In migratory sheets, traction forces and supracellular tensions are highly heterogeneous because a mechanical wave propagates from the tissue edge and crosses intercellular junctions, in which each cell transmits forces to the cells behind after an initial pull of the free edge on the substrate (Serra-Picamal et al., 2012). These anisotropies in tension, which depend upon an ordered cytoskeleton, help generate leader cells, thereby contributing to supracellular polarity (Poujade et al., 2007; Revenu et al., 2014); leaders then guide follower cells, which can be organised as either small cohorts (Reffay et al., 2014) or as an entire sheet. Accompanying the large-scale tissue polarisation are long-range coordinated supracellular cell movements (Poujade et al., 2007; Vedula et al., 2012) that contribute to bulk movement of cells.

The cytoskeleton is also highly organised during embryonic wound healing (Fig. 4E) (Abreu-Blanco et al., 2012b), and sometimes also during adult wound healing (Danjo and Gipson, 1998; Grootjans et al., 2011; Russo et al., 2005). After wounding in the *Drosophila* pupal notum, a pulse of actomyosin filaments flows from several cell rows back toward the wound margin (Antunes et al., 2013), which may be controlled by a wave of Ca^{2+} moving in the same direction (Shannon et al., 2017). These actomyosin filaments assemble into a supracellular actomyosin cable at the wound edge that has previously been proposed to aid collective movement by acting as a 'purse string' that closes the wound (Martin and Lewis, 1992). That being said, cable formation is dispensable for *Drosophila* dorsal closure, a model for wound healing (Ducuing and Vincent, 2016). Instead, it has been suggested that heterogeneous contraction of the actomyosin cable coordinates the movements of cells at the wound edge, which leads to rapid wound repair (Abreu-Blanco et al., 2012a; Ducuing and Vincent, 2016; Fernandez-Gonzalez and Zallen, 2013; Wood et al., 2002; Zulueta-Coarasa and Fernandez-Gonzalez, 2018). Nonetheless, although contraction itself might not be a supracellular event, in that neighbours do not always synchronously contract together, normal (unscarred) healing requires a supracellular actin cable structure (Ducuing and Vincent, 2016), indicating that there is high coordination between cells when individuals contract. Here again, supracellular structures such an actomyosin cable co-exists with the formation of protrusions by cells around the wound during wound healing.

Another example of a cell population that has many aspects of supracellularity is the neural crest, a stem cell population that migrates large distances in the developing embryo to contribute to several tissues. The cranial neural crest of *Xenopus* and zebrafish embryos migrates collectively in response to chemoattractants, such as SDF1 (Shellard and Mayor, 2016; Theveneau et al., 2010), by polarising at the level of the entire cluster. Supracellular polarity is imposed through CIL (Carmona-Fontaine et al., 2008; Yoon et al., 2018), the phenomenon of pairs of colliding cells repolarising and move awaying from each other (Roycroft and Mayor, 2016; Stramer and Mayor, 2017). In a cluster of high cell density, CIL causes outward protrusions to be formed at the free edge, but not internally, thereby contributing to the polarity of the entire cluster (Carmona-Fontaine et al., 2008). There is also cytoskeletal organisation at the cluster level: cells at the edge of the group are connected by a supracellular tensile actomyosin cable that appears to be mechanically coupled between adjacent cells via N-cadherin (Shellard et al., 2018). The neural crest also exhibits supracellular forces that enable it to move. Protrusions generate large traction forces at the cell periphery, but not in the middle of the group (Roycroft et al., 2018; Scarpa et al., 2015); this means that CIL controls supracellular polarity and force generation. However, how traction forces are transmitted across the entire cell cluster is unclear. During directed migration, supracellular polarity is promoted by SDF1-dependent activation of Rac1 in front cells (Theveneau et al., 2010) and inhibition of actomyosin contractility in front cells (Shellard et al., 2018). The actomyosin cable contracts in a supracellular manner, in that multiple adjacent cells all contract synchronously. These supracellular contractile forces cause a tissue-scale flow of cell movements, whereby rear cells move to the front and cells at the edge of the group are mechanically pulled rearwards (Fig. 4F) (Shellard et al., 2018). The coordination between all these factors results in a cell cluster that migrates in a highly efficient manner that cannot be explained by considering only its individual constituent cells.

Full supracellular migration

'Complete' or full supracellular behaviour refers to a system in which the individual cells per se are not required for tissue movement. In this sense, full supracellular migration would present itself as a group of cells moving in such a way that the presence of cell membranes exists only to limit the cell boundary, but that they are redundant for the bulk movement of the group. In this case, removal of the cell membranes should only cause loss of cell–cell adhesion and not affect movement of the tissue mass itself. This would demonstrate that it is the activity of the tissue as a whole, and not the individual components, which best explain tissue movement. An example of such supracellular behaviour is the folding of epithelial sheets. During ventral furrow formation in *Drosophila*, myosin II becomes phosphorylated at the apical surfaces of cells; this causes an anisotropic constriction that drives tissue invagination, leading to a mass inward-movement of cells (Fig. 4G) (He et al., 2014; Martin et al., 2010; Martin and Goldstein, 2014; Monier et al., 2015). Here, tissue movement corresponds to, and behaves like, that of an entirely viscous fluid, despite the existence of sub-cellular structures, organelles and cell boundaries (He et al., 2014). Even acellularised embryos exhibit fluid motility similar to that in the wild type (He et al., 2014). Furthermore, the degree of apical constriction is correlated with fluid flow velocity (He et al., 2014), and specific activation of apical constriction (by inducing its activator, Rho) is sufficient to reconstitute epithelial folding by inducing apical constriction (Izquierdo et al., 2018). The mechanical integration of the apical surface drives a collective integrated shape change that translocates the tissue mass. This morphogenic process can therefore be considered a truly supracellular event, in which all invaginating epithelial cells behave as a totally cohesive single entity.

Journal of Cell Science (2019) 132, jcs226142. doi:10.1242/jcs.226142

Considering collectives as 'supracells'

Based on the considerations above, we argue that some biological processes that have traditionally been explained at a cellular level may be better understood using the concept of supracellular behaviour; in the grand-scheme of morphogenetic movement, the actions of individual cells may be irrelevant, as discussed in some specific examples below.

Amphibian gastrulation

Amphibian gastrulation (Fig. 5A) is typically viewed as a highly complex process that not only involves, but requires, precise cell re-arrangements. However, when the mechanics of gastrulation were initially characterised, the gastrulating embryo was considered to be like a 'supracell'. Walter Vogt, who was the first to have this idea about the gastrula, remarked that "it does not appear at all as if cells were working in the sense that single part-movements were combining to form the movements of masses; for even the most natural and plausible explanation by means of amoeboid motion of single cells fails utterly" (Vogt, 1923). The idea that the gastrulating embryo should be considered at a level greater than the cell was later commented on, and investigated, by Johannes Holtfreter, who, when trying to understand the movements of gastrulation, wondered "if there might not exist a 'superior force' supervising and direct the single part-movements" (Holtfreter, 1943).

One morphogenetic process that occurs during early amphibian gastrulation is epiboly, in which the cells at one end of the embryo, the animal hemisphere, spread by thinning, which then expands the tissue. Simultaneously, a structure called the blastopore, a groove into the gastrula in which mesoderm is internalised, is formed at the opposite side of the embryo, the vegetal hemisphere (Wen and Winklbauer, 2017) (Fig. 5A). These seemingly complex morphogenic movements can be recapitulated in unfertilised amphibian (single-cell) eggs incubated in a hypertonic solution (Fig. 5B): the pigmented animal cap surface expands over the vegetal pole and there is shrinkage of the vegetal pole (Holtfreter, 1943; Smith and Ecker, 1970). It is unclear how exactly this 'pseudogastrulation' mimics epiboly and blastopore formation of gastrulae, but it may reflect the quantity or activity of cytoskeletal components in the animal and vegetal regions, and thus be related to the relaxation of the animal cap epithelium during epiboly and the

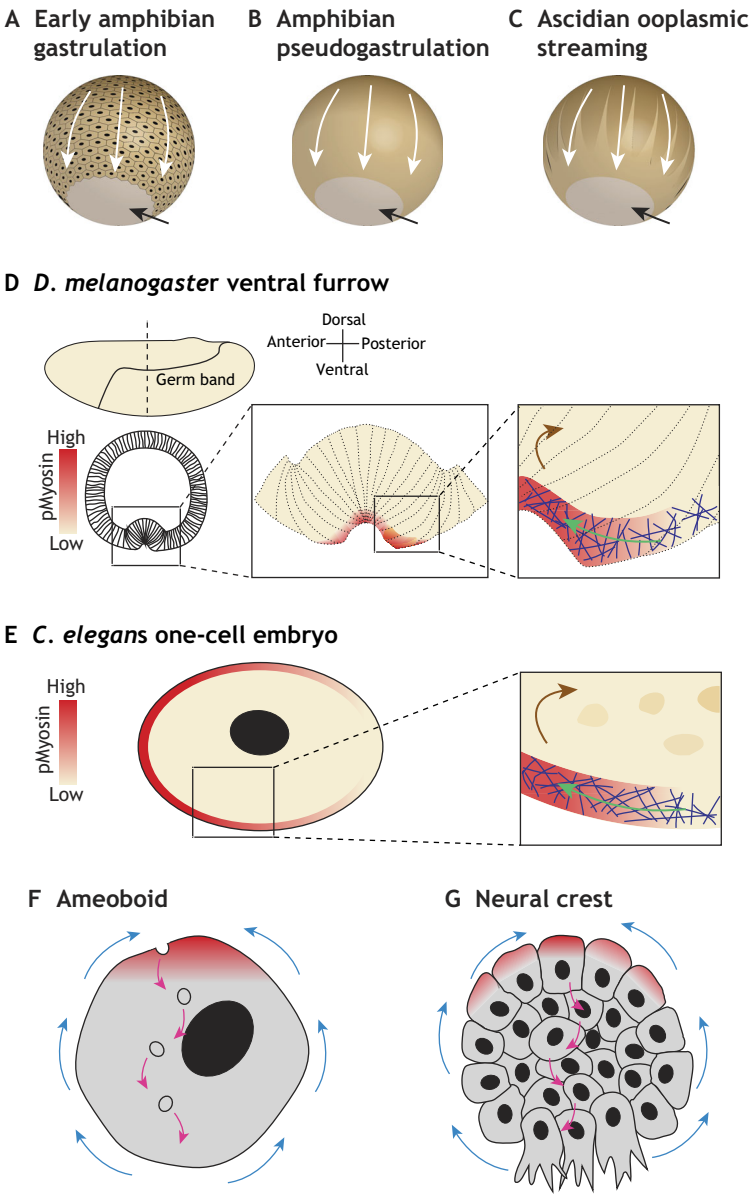

Fig. 5. Examples of 'supracell' movements. (A) Early amphibian gastrulation involves spreading and thinning of the cell layers in the animal hemisphere, termed epiboly (white arrows), and invagination of tissues in the opposite vegetal hemisphere, called blastopore formation (black arrow). (B) Amphibian pseudogastrulation in oocytes bears similarities to early gastrulation as it recapitulates some morphogenetic events, such as epiboly (white arrows) of the animal pole (dark brown) over the vegetal pole (light brown), and blastopore formation (black arrow). (C) Another movement that is similar to epiboly is that observed during normal cytoplasmic streaming, immediately after ascidian fertilisation in the one-cell stage embryo, whereby cytoplasm at one end of the embryo moves (white arrow) toward the vegetal region (black arrow). Therefore, all these three processes (panels A–C) could be considered examples of supracellular movement. (D) Gastrulation in *Drosophila* involves the formation of a ventral furrow through the invagination of a single cell epithelial layer. Invagination is dependent on high levels of phosphorylated myosin (in red) at the apical side. Cell membranes are redundant for this process (dashed lines). Collective movement relies on a supracellular actin network that is associated with actin filaments of the cortex (blue lines in the inset), which contracts (green arrow). This results in the cells being passively pushed down and outwards (brown arrow). (E) Analogous contractility of the cortex in the one-cell zygote of *C. elegans*; here a gradient of phosphorylated myosin along the anterior–posterior axis of the cell cortex causes contraction, which results in cytoplasmic streaming (brown arrow). (F) Single-cell amoeba can migrate by 'swimming' or without strong adhesions. Retrograde flow of the cell membrane (blue arrows) is a consequence of high RhoA activity (red) at the rear, which drives the cell forward. Cell shape is maintained as a result of anterograde trafficking of rear components (pink arrows). Note that forward movement is toward the bottom of the panel. (G) The cluster behaviour of the *Xenopus* and zebrafish cranial neural crest, which migrates as a 'supracell', is analogous to the amoeboid mode of 'swimming'. Here, collective neural crest cell chemotaxis relies on high RhoA levels at the rear of the cluster, which contracts a supracellular actomyosin cable, thereby causing the retrograde flow of peripheral cells (blue arrows). Cells at the rear intercalate with their neighbours and so move forward (pink arrows).

shrinkage of the vegetal region during blastopore formation. Thus, seemingly complex morphogenesis may not be the result of the action of individual cells, but rather a consequence of the activity of a complex and far-reaching protein network. An obvious candidate is the actin cortex, because it controls cell shape and can generate forces on the cell surface across both short and long distances.

Streaming movements of epiboly, such as those in amphibian gastrulae and pseudogastrulating eggs, also occur in newly fertilised ascidian embryos (Conklin, 1905; Costello, 1948). Initially, the ascidian oocyte has a yellow cortical cytoplasm surrounding the grey yolky inner cytoplasm. After fertilisation, the yellow cortical cytoplasm and clear cytoplasm that is derived from the breakdown of the oocyte nucleus contract vegetally; this results in ooplasmic streaming (Fig. 5C), whereby the surface of the embryo is covered by grey cytoplasm. This movement is like epiboly in gastrulating embryos. The similarity between this bulk movement and those in gastrulation and pseudogastrulation suggest that the events of early gastrulation could be considered highly supracellular events, where its cellular components are not actively driving the morphogenetic changes, but rather an extensive cytoskeletal cortex orchestrates these events in a timely manner. Unfortunately, there have been no functional studies to analyse the process of pseudogastrulation, and it would therefore be interesting to see whether the early gastrulation-like movements of epiboly and blastopore formation are indeed due to a cytoskeletal network, which could potentially be equivalent to a supracellular network found during normal gastrulation. If a far-spanning actin cortical network is responsible for these morphogenetic events, this would suggest that during cellularisation, the formation of supracellular actomyosin cables and meshworks are a means for how cells overcome the 'obstacle' of a membrane separating the cortical components of adjacent cells.

Drosophila ventral furrow formation

A supracellular apical actin meshwork is the driver of epithelial invagination (a supracellular shape change and translocation) during formation of the ventral furrow in *Drosophila* embryos (Martin et al., 2010). This causes a flow of cytoplasm that resembles a laminar flow, in that when the cortex constricts and moves, the underlying cytoplasm is dragged with it (He et al., 2014). This flow is reproduced in acellular embryos (Fig. 5D). The cytoplasmic flow matches the flow of the plasma membrane, indicating that the cell membrane moves passively as a consequence of the cytoplasmic flow, and the membrane does not offer any driving force or resistance (He et al., 2014). Thus, the cell membranes are dispensable for cytoplasmic redistribution and collective movement. These actin-driven flow patterns are reminiscent of flows that have been predicted for individually migrating cells, according to the theory of active gels (Kruse et al., 2004; Voituriez et al., 2006), and analogous to cytoplasmic streaming in single cells, such as algal cells and the *Drosophila* syncytium (Glotzer et al., 1997; Goldstein et al., 2008), whose rotational streaming patterns are very similar and caused by the activity of actin and microtubules. Furthermore, the hydrodynamic properties of the cytoplasm in response to cortical forces during *Drosophila* furrow morphogenesis show identical cytoplasmic flows to those observed in the one-cell stage *Caenorhabditis elegans* embryo (Fig. 5E) in response to the action of actomyosin motors in the cell cortex (Niwayama et al., 2011). These observations suggest that furrow morphogenesis may be better explained using the notion of a 'supracell' (Fig. 1C) than the traditional concept of individualistic collective cell migration.

Neural crest migration

The collective movement of *Xenopus* and zebrafish neural crest cells also appear to act as a giant 'supracell' that is analogous to the rear-driven motility of amoeboid migration. Amoeboid cells, such as neutrophils and *Dictyostelium*, can propel themselves through viscous liquids and along non-adhesive substrates by generating high levels of actomyosin-driven cortical contractility at the cell rear (Barry and Bretscher, 2010; Bergert et al., 2015; Hawkins et al., 2009; Lim et al., 2013; O'Neill et al., 2018; Paluch et al., 2016; Tanaka et al., 2017; Tozluoglu et al., 2013). This mode of single-cell migration is controlled by active RhoA at the cell rear, which can drive rearward-membrane flow (Fig. 5F). Likewise, collective neural crest chemotaxis is dependent on high RhoA levels in the rear cells of the cluster, which generates a rearward flow of outer cells (blue arrows in Fig. 5G) (Shellard et al., 2018). To maintain cell size and shape, amoebae use their endocytic machinery to traffic membrane to the front (O'Neill et al., 2018). Likewise, a wave of anterograde cell movement emanates forward from the rear during neural crest migration (red arrows in Fig. 5G) (Shellard et al., 2018). Mechanistically, movement in the two systems is based on the actomyosin network: in amoebae, there is a retrograde flow of the cortical actin network (Liu et al., 2015; Maiuri et al., 2015), while in neural crest cell groups, a supracellular actomyosin cable connects the outer rim (Shellard et al., 2018). In both cases, anisotropies in contractile forces drive the cell(s) forward.

Altogether, these findings suggest that systems that have previously been rationalised based on the activities of individual cells may be better explained by considering the behaviour of the tissue as a whole.

Perspectives

New insights into collective migration have returned the historic idea of supracellular motility to the fore. It is now becoming increasingly evident that many systems appear to incorporate supracellular features to achieve efficient movement, and this theme might further emerge from future research. For example, it is feasible to consider that there may be supracellular coupling of actomyosin across cell junctions in the early pre-implantation mouse embryo, because the cortex of adjacent cells is connected by cytoskeletal actin, and pulsatile contraction of the blastomeres is driven by the apical actomyosin cortex (Fierro-Gonzalez et al., 2013; Maître et al., 2015; Mayor et al., 1989). Nevertheless, many interesting questions remain, such as how are supracellular cytoskeletons effectively organised between masses of cells? In addition to supracellular coordination originating from a connected cytoskeleton and from signals that emerge from cell–cell adhesions, another source of supracellular regulation is likely to arise from gap junction proteins (e.g. connexins), because moving cell groups often maintain cell–cell communication. However, how signalling propagation through gap junctions contributes to polarity and the mechanical connection between moving cells remains unclear (Defranco et al., 2008; Kotini et al., 2018). Addressing these questions may further elucidate other ways in which collectively migrating cell groups coordinate their activities efficiently at the supracellular level.

Competing interests

The authors declare no competing or financial interests.

Funding

Work in R.M. laboratory is supported by grants from the Medical Research Council (MR/S007792/1), Biotechnology and Biological Sciences Research Council (M008517) and Wellcome Trust (102489/Z/13/Z).

References

Abreu-Blanco, M. T., Verboon, J. M., Liu, R., Watts, J. J. and Parkhurst, S. M. (2012a). Drosophila embryos close epithelial wounds using a combination of

cellular protrusions and an actomyosin purse string. *J. Cell Sci.* **125**, 5984-5997. doi:10.1242/jcs.109066

Abreu-Blanco, M. T., Watts, J. J., Verboon, J. M. and Parkhurst, S. M. (2012b). Cytoskeleton responses in wound repair. *Cell. Mol. Life Sci.* **69**, 2469-2483. doi:10.1007/s00018-012-0928-2

Antunes, M., Pereira, T., Cordeiro, J. V., Almeida, L. and Jacinto, A. (2013). Coordinated waves of actomyosin flow and apical cell constriction immediately after wounding. *J. Cell Biol.* **202**, 365-379. doi:10.1083/jcb.201211039

Arima, S., Nishiyama, K., Ko, T., Arima, Y., Hakozaki, Y., Sugihara, K., Koseki, H., Uchijima, Y., Kurihara, Y. and Kurihara, H. (2011). Angiogenic morphogenesis driven by dynamic and heterogeneous collective endothelial cell movement. *Development* **138**, 4763-4776. doi:10.1242/dev.068023

Baker, J. R. (1948). The cell-theory-a restatement, history, and critique.1. *Q J. Microsc. Sci.* **89**, 103-125.

Barlan, K., Cetera, M. and Horne-Badovinac, S. (2017). Fat2 and lar define a basally localized planar signaling system controlling collective cell migration. *Dev. Cell* **40**, 467-477. doi:10.1016/j.devcel.2017.02.003

Barry, N. P. and Bretscher, M. S. (2010). Dictyostelium amoebae and neutrophils can swim. *Proc. Natl. Acad. Sci. USA* **107**, 11376-11380. doi:10.1073/pnas.1006327107

Barry, A. K., Wang, N. and Leckband, D. E. (2015). Local VE-cadherin mechanotransduction triggers long-ranged remodeling of endothelial monolayers. *J. Cell Sci.* **128**, 1341-1351. doi:10.1242/jcs.159954

Bateman, J., Reddy, R. S., Saito, H. and Van Vactor, D. (2001). The receptor tyrosine phosphatase Dlar and integrins organize actin filaments in the Drosophila follicular epithelium. *Curr. Biol.* **11**, 1317-1327. doi:10.1016/S0960-9822(01)00420-1

Bazellieres, E., Conte, V., Elosegui-Artola, A., Serra-Picamal, X., Bintanel-Morcillo, M., Roca-Cusachs, P., Munoz, J. J., Sales-Pardo, M., Guimera, R. and Trepat, X. (2015). Control of cell-cell forces and collective cell dynamics by the intercellular adhesome. *Nat. Cell Biol.* **17**, 409. doi:10.1038/ncb3135

Behrndt, M., Salbreux, G., Campinho, P., Hauschild, R., Oswald, F., Roensch, J., Grill, S. W. and Heisenberg, C. P. (2012). Forces driving epithelial spreading in zebrafish gastrulation. *Science* **338**, 257-260. doi:10.1126/science.1224143

Bergert, M., Erzberger, A., Desai, R. A., Aspalter, I. M., Oates, A. C., Charras, G., Salbreux, G. and Paluch, E. K. (2015). Force transmission during adhesion-independent migration. *Nat. Cell Biol.* **17**, 524. doi:10.1038/ncb3134

Bertet, C., Sulak, L. and Lecuit, T. (2004). Myosin-dependent junction remodelling controls planar cell intercalation and axis elongation. *Nature* **429**, 667-671. doi:10.1038/nature02590

Bianco, A., Poukkula, M., Cliffe, A., Mathieu, J., Luque, C. M., Fulga, T. A. and Rørth, P. (2007). Two distinct modes of guidance signalling during collective migration of border cells. *Nature* **448**, U362-U12. doi:10.1038/nature05965

Blankenship, J. T., Backovic, S. T., Sanny, J. S. P., Weitz, O. and Zallen, J. A. (2006). Multicellular rosette formation links planar cell polarity to tissue morphogenesis. *Dev. Cell* **11**, 459-470. doi:10.1016/j.devcel.2006.09.007

Blaser, H., Reichman-Fried, M., Castanon, I., Dumstrei, K., Marlow, F. L., Kawakami, K., Solnica-Krezel, L., Heisenberg, C.-P. and Raz, E. (2006). Migration of zebrafish primordial germ cells: a role for myosin contraction and cytoplasmic flow. *Dev. Cell* **11**, 613-627. doi:10.1016/j.devcel.2006.09.023

Bourne, G. C. (1895). A criticism of the cell-theory; being an answer to Mr. Sedgwick's article on the inadequacy of the cellular theory of development. *J. Cell Sci.* **s2-38**, 137-174.

Brugues, A., Anon, E., Conte, V., Veldhuis, J., Gupta, M., Colombelli, J., Muñoz, J., Brodland, G., Ladoux, B. and Trepat, X. (2014). Forces driving epithelial wound healing. *Mol. Biol. Cell* **10**, 683-690. doi:10.1038/nphys3040

Cai, D., Chen, S.-C., Prasad, M., He, L., Wang, X., Choesmel-Cadamuro, V., Sawyer, J. K., Danuser, G. and Montell, D. J. (2014). Mechanical feedback through E-cadherin promotes direction sensing during collective cell migration. *Cell* **157**, 1146-1159. doi:10.1016/j.cell.2014.03.045

Carmona-Fontaine, C., Matthews, H. K., Kuriyama, S., Moreno, M., Dunn, G. A., Parsons, M., Stern, C. D. and Mayor, R. (2008). Contact inhibition of locomotion in vivo controls neural crest directional migration. *Nature* **456**, 957-961. doi:10.1038/nature07441

Cetera, M., Leybova, L., Joyce, B. and Devenport, D. (2018). Counter-rotational cell flows drive morphological and cell fate asymmetries in mammalian hair follicles. *Nat. Cell Biol.* **20**, 541. doi:10.1038/s41556-018-0082-7

Chen, D.-Y., Lipari, K. R., Dehghan, Y., Streichan, S. J. and Bilder, D. (2016). Symmetry breaking in an edgeless epithelium by Fat2-regulated microtubule polarity. *Cell Rep.* **15**, 1125-1133. doi:10.1016/j.celrep.2016.04.014

Combedazou, A., Choesmel-Cadamuro, V., Gay, G., Liu, J. Y., Dupre, L., Ramel, D. and Wang, X. B. (2017). Myosin II governs collective cell migration behaviour downstream of guidance receptor signalling. *J. Cell Sci.* **130**, 97-103. doi:10.1242/jcs.179952

Conklin, E. G. (1905). The organization and cell-lineage of the ascidian egg. *J. Acad. Nat. Sci. of Phila.* **13**, doi: 10.5962/bhl.title.4801. doi: 10.5962/bhl.title.4801

Coravos, J. S., Mason, F. M. and Martin, A. C. (2017). Actomyosin Pulsing in tissue integrity maintenance during morphogenesis. *Trends Cell Biol.* **27**, 276-283. doi:10.1016/j.tcb.2016.11.008

Costello, D. P. (1948). Ooplasmic segregation in relation to differentiation. *Ann. N. Y. Acad. Sci.* **49**, 663-683. doi:10.1111/j.1749-6632.1948.tb30960.x

Cui, C., Yang, X. S., Chuai, M. L., Glazier, J. A. and Weijer, C. J. (2005). Analysis of tissue flow patterns during primitive streak formation in the chick embryo. *Dev. Biol.* **284**, 37-47. doi:10.1016/j.ydbio.2005.04.021

Danjo, Y. and Gipson, I. K. (1998). Actin 'purse string' filaments are anchored by E-cadherin-mediated adherens junctions at the leading edge of the epithelial wound, providing coordinated cell movement. *J. Cell Sci.* **111**, 3323-3332.

Das, T., Safferling, K., Rausch, S., Grabe, N., Boehm, H. and Spatz, J. P. (2015). A molecular mechanotransduction pathway regulates collective migration of epithelial cells. *Nat. Cell Biol.* **17**, 276. doi:10.1038/ncb3115

Defranco, B. H., Nickel, B., Baty, C., Martinez, J., Gay, V., Sandulache, V., Hackam, D. and Murray, S. (2008). Migrating Cells Retain Gap Junction Plaque Structure and Function. *Cell Commun. Adhes.* **15**, 273-288. doi:10.1080/15419060802198298

Doitsidou, M., Reichman-Fried, M., Stebler, J., Köprunner, M., Dörries, J., Meyer, D., Esguerra, C. V., Leung, T. and Raz, E. (2002). Guidance of primordial germ cell migration by the chemokine SDF-1. *Cell* **111**, 647-659. doi:10.1016/S0092-8674(02)01135-2

Dona, E., Barry, J. D., Valentin, G., Quirin, C., Khmelinskii, A., Kunze, A., Durdu, S., Newton, L. R., Fernandez-Minan, A., Huber, W. et al. (2013). Directional tissue migration through a self-generated chemokine gradient. *Nature* **503**, 285. doi:10.1038/nature12635

du Roure, O., Saez, A., Buguin, A., Austin, R. H., Chavrier, P., Silberzan, P. and Ladoux, B. (2005). Force mapping in epithelial cell migration. *Proc. Natl. Acad. Sci. USA* **102**, 2390-2395. doi:10.1073/pnas.0408482102

Duchek, P., Somogyi, K., Jékely, G., Beccari, S. and Rørth, P. (2001). Guidance of cell migration by the Drosophila PDGF/VEGF receptor. *Cell* **107**, 17-26. doi:10.1016/S0092-8674(01)00502-5

Ducuing, A. and Vincent, S. (2016). The actin cable is dispensable in directing dorsal closure dynamics but neutralizes mechanical stress to prevent scarring in the Drosophila embryo. *Nat. Cell Biol.* **18**, 1149. doi:10.1038/ncb3421

Edwards, K. A. and Kiehart, D. P. (1996). Drosophila nonmuscle myosin II has multiple essential roles in imaginal disc and egg chamber morphogenesis. *Development* **122**, 1499-1511.

Farooqui, R. and Fenteany, G. (2005). Multiple rows of cells behind an epithelial wound edge extend cryptic lamellipodia to collectively drive cell-sheet movement. *J. Cell Sci.* **118**, 51-63. doi:10.1242/jcs.01577

Fernandez-Espartero, C. H., Ramel, D., Farago, M., Malartre, M., Luque, C. M., Limanovich, S., Katzav, S., Emery, G. and Martin-Bermudo, M. D. (2013). GTP exchange factor Vav regulates guided cell migration by coupling guidance receptor signalling to local Rac activation. *J. Cell Sci.* **126**, 2285-2293. doi:10.1242/jcs.124438

Fernandez-Gonzalez, R. and Zallen, J. A. (2013). Wounded cells drive rapid epidermal repair in the early Drosophila embryo. *Mol. Biol. Cell* **24**, 3227-3237. doi:10.1091/mbc.e13-05-0228

Fierro-Gonzalez, J. C., White, M. D., Silva, J. C. and Plachta, N. (2013). Cadherin-dependent filopodia control preimplantation embryo compaction. *Nat. Cell Biol.* **15**, 1424. doi:10.1038/ncb2875

Franke, J. D., Montague, R. A. and Kiehart, D. P. (2005). Nonmuscle myosin II generates forces that transmit tension and drive contraction in multiple tissues during dorsal closure. *Curr. Biol.* **15**, 2208-2221. doi:10.1016/j.cub.2005.11.064

Friedl, P. and Gilmour, D. (2009). Collective cell migration in morphogenesis, regeneration and cancer. *Nat. Rev. Mol. Cell Biol.* **10**, 445-457. doi:10.1038/nrm2720

Friedl, P., Wolf, K. and Zegers, M. M. (2014). Rho-directed forces in collective migration. *Nat. Cell Biol.* **16**, 208-210. doi:10.1038/ncb2923

Gaggioli, C., Hooper, S., Hidalgo-Carcedo, C., Grosse, R., Marshall, J. F., Harrington, K. and Sahai, E. (2007). Fibroblast-led collective invasion of carcinoma cells with differing roles for RhoGTPases in leading and following cells. *Nat. Cell Biol.* **9**, 1392-1U92. doi:10.1038/ncb1658

Gerhardt, H., Golding, M., Fruttiger, M., Ruhrberg, C., Lundkvist, A., Abramsson, A., Jeltsch, M., Mitchell, C., Alitalo, K., Shima, D. et al. (2003). VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J. Cell Biol.* **161**, 1163-1177. doi:10.1083/jcb.200302047

Gerould, J. H. (1922). The dawn of the cell theory. *Scientific Monthly* **14**, 268-277.

Glotzer, J. B., Saffrich, R., Glotzer, M. and Ephrussi, A. (1997). Cytoplasmic flows localize injected oskar RNA in Drosophila oocytes. *Curr. Biol.* **7**, 326-337. doi:10.1016/S0960-9822(06)00156-4

Goldstein, R. E., Tuval, I. and van de Meent, J. W. (2008). Microfluidics of cytoplasmic streaming and its implications for intracellular transport. *Proc. Natl. Acad. Sci. USA* **105**, 3663-3667. doi:10.1073/pnas.0707223105

Good, M. and Trepat, X. (2018). Cell parts to complex processes, from the bottom up. *Nature* **563**, 188-189. doi:10.1038/d41586-018-07246-8

Grootjans, J., Thuijls, G., Derikx, J. P. M., van Dam, R. M., Dejong, C. H. C. and Buurman, W. A. (2011). Rapid lamina propria retraction and zipper-like constriction of the epithelium preserves the epithelial lining in human small intestine exposed to ischaemia-reperfusion. *J. Pathol.* **224**, 411-419. doi:10.1002/path.2882

Gutzeit, H. O. (1990). The microfilament pattern in the somatic follicle cells of mid-vitellogenic ovarian follicles of Drosophila. *Eur. J. Cell Biol.* **53**, 349-356.
Hawkins, R. J., Piel, M., Faure-Andre, G., Lennon-Dumenil, A. M., Joanny, J. F., Prost, J. and Voituriez, R. (2009). Pushing off the walls: a mechanism of cell motility in confinement. *Phys. Rev. Lett.* **102**, 058103. doi:10.1103/PhysRevLett.102.058103
He, L., Wang, X. B., Tang, H. L. and Montell, D. J. (2010). Tissue elongation requires oscillating contractions of a basal actomyosin network. *Nat. Cell Biol.* **12**, 1133-1U40. doi:10.1038/ncb2124
He, B., Doubrovinski, K., Polyakov, O. and Wieschaus, E. (2014). Apical constriction drives tissue-scale hydrodynamic flow to mediate cell elongation. *Nature* **508**, 392. doi:10.1038/nature13070
Hegerfeldt, Y., Tusch, M., Brocker, E. B. and Friedl, P. (2002). Collective cell movement in primary melanoma explants: Plasticity of cell-cell interaction, ss 1-integrin function, and migration strategies. *Cancer Res.* **62**, 2125-2130.
Hellström, M., Phng, L.-K., Hofmann, J. J., Wallgard, E., Coultas, L., Lindblom, P., Alva, J., Nilsson, A.-K., Karlsson, L., Gaiano, N. et al. (2007). Dll4 signalling through Notch1 regulates formation of tip cells during angiogenesis. *Nature* **445**, 776-780. doi:10.1038/nature05571
Hidalgo-Carcedo, C., Hooper, S., Chaudhry, S. I., Williamson, P., Harrington, K., Leitinger, B. and Sahai, E. (2011). Collective cell migration requires suppression of actomyosin at cell-cell contacts mediated by DDR1 and the cell polarity regulators Par3 and Par6. *Nat. Cell Biol.* **13**, U49-U123. doi:10.1038/ncb2133
Holtfreter, J. (1943). A study of the mechanics of gastrulation Part I. *J. Exp. Zool.* **94**, 261-318. doi:10.1002/jez.1400940302
Irvine, K. D. and Wieschaus, E. (1994). Cell intercalation during drosophila germband extension and its regulation by pair-rule segmentation genes. *Development* **120**, 827-841.
Izquierdo, E., Quinkler, T. and De Renzis, S. (2018). Guided morphogenesis through optogenetic activation of Rho signalling during early Drosophila embryogenesis. *Nat. Commun.* **9**, 2366. doi:10.1038/s41467-018-04754-z
Jacinto, A., Wood, W., Balayo, T., Turmaine, M., Martinez-Arias, A. and Martin, P. (2000). Dynamic actin-based epithelial adhesion and cell matching during Drosophila dorsal closure. *Curr. Biol.* **10**, 1420-1426. doi:10.1016/S0960-9822(00)00796-X
Jacques, E., Verbelen, J. P. and Vissenberg, K. (2013). Mechanical stress in Arabidopsis leaves orients microtubules in a 'continuous' supracellular pattern. *BMC Plant Biol.* **13**, 163. doi:10.1186/1471-2229-13-163
Jakobsson, L., Franco, C. A., Bentley, K., Collins, R. T., Ponsioen, B., Aspalter, I. M., Rosewell, I., Busse, M., Thurston, G., Medvinsky, A. et al. (2010). Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting. *Nat. Cell Biol.* **12**, 943-953. doi:10.1038/ncb2103
Kim, J. H., Serra-Picamal, X., Tambe, D. T., Zhou, E. H. H., Park, C. Y., Sadati, M., Park, J.-A., Krishnan, R., Gweon, B., Millet, E. et al. (2013). Propulsion and navigation within the advancing monolayer sheet. *Nat. Mater.* **12**, 856-863. doi:10.1038/nmat3689
Kim, H., Muller, K., Shardt, O., Afkhami, S. and Stone, H. A. (2017). Solutal Marangoni flows of miscible liquids drive transport without surface contamination. *Nat. Phys.* **13**, 1105. doi:10.1038/nphys4214
Kotini, M., Barriga, E. H., Leslie, J., Gentzel, M., Rauschenberger, V., Schambon, A. and Mayor, R. (2018). Gap junction protein Connexin-43 is a direct transcriptional regulator of N-cadherin in vivo. *Nat. Commun.* **9**, 3846. doi:10.1038/s41467-018-06368-x
Kruse, K., Joanny, J. F., Julicher, F., Prost, J. and Sekimoto, K. (2004). Asters, vortices, and rotating spirals in active gels of polar filaments. *Phys. Rev. Lett.* **92**, 078101. doi:10.1103/PhysRevLett.92.078101
Labernadie, A., Kato, T., Brugués, A., Serra-Picamal, X., Derzsi, S., Arwert, E., Weston, A., González-Tarragó, V., Elosegui-Artola, A., Albertazzi, L. et al. (2017). A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion. *Nat. Cell Biol.* **19**, 224-237. doi:10.1038/ncb3478
Ladoux, B., Mège, R.-M. and Trepat, X. (2016). Front-rear polarization by mechanical cues: from sincle cells to tissues. *Trends Cell Biol.* **26**, 420-433. doi:10.1016/j.tcb.2016.02.002
Lawton, A. K., Nandi, A., Stulberg, M. J., Dray, N., Sneddon, M. W., Pontius, W., Emonet, T. and Holley, S. A. (2013). Regulated tissue fluidity steers zebrafish body elongation. *Development* **140**, 573-582. doi:10.1242/dev.090381
Lim, F. Y., Koon, Y. L. and Chiam, K.-H. (2013). A computational model of amoeboid cell migration. *Comput. Methods Biomech. Biomed. Engin.* **16**, 1085-1095. doi:10.1080/10255842.2012.757598
Liu, Y.-J., Le Berre, M., Lautenschlaeger, F., Maiuri, P., Callan-Jones, A., Heuze, M., Takaki, T., Voituriez, R. and Piel, M. (2015). Confinement and low adhesion induce fast amoeboid migration of slow mesenchymal cells. *Cell* **160**, 659-672. doi:10.1016/j.cell.2015.01.007
Luyet, B. J. (1940). The case against the cell theory. *Science* **91**, 252-255. doi:10.1126/science.91.2359.252
Maître, J. L., Niwayama, R., Turlier, H., Nédélec, F. and Hiiragi, T. (2015). Pulsatile cell-autonomous contractility drives compaction in the mouse embryo. *Nat. Cell Biol.* **17**, 849-855. doi:10.1038/ncb3185
Maiuri, P., Rupprecht, J.-F., Wieser, S., Ruprecht, V., Bénichou, O., Carpi, N., Coppey, M., De Beco, S., Gov, N., Heisenberg, C. P. et al. (2015). Actin flows mediate a universal coupling between cell speed and cell persistence. *Cell* **161**, 374-386. doi:10.1016/j.cell.2015.01.056
Malet-Engra, G., Yu, W. M., Oldani, A., Rey-Barroso, J., Gov, N. S., Scita, G. and Dupré, L. (2015). Collective cell motility promotes chemotactic prowess and resistance to chemorepulsion. *Curr. Biol.* **25**, 242-250. doi:10.1016/j.cub.2014.11.030
Martin, A. C. and Goldstein, B. (2014). Apical constriction: themes and variations on a cellular mechanism driving morphogenesis. *Development* **141**, 1987-1998. doi:10.1242/dev.102228
Martin, P. and Lewis, J. (1992). Actin cables and epidermal movement in embryonic wound-healing. *Nature* **360**, 179-183. doi:10.1038/360179a0
Martin, A. C., Gelbart, M., Fernandez-Gonzalez, R., Kaschube, M. and Wieschaus, E. F. (2010). Integration of contractile forces during tissue invagination. *J. Cell Biol.* **188**, 735-749. doi:10.1083/jcb.200910099
Mayor, R. and Etienne-Manneville, S. (2016). The front and rear of collective cell migration. *Nat. Rev. Mol. Cell Biol.* **17**, 97-109. doi:10.1038/nrm.2015.14
Mayor, R., Pey, R. and Izquierdo, L. (1989). Development of cytoskeletal connections between cells of preimplantation mouse embryos. *Rouxs Archives of Developmental Biology* **198**, 233-241. doi:10.1007/BF00375910
McDonald, J. A., Pinheiro, E. M., Kadlec, L., Schupbach, T. and Montell, D. J. (2006). Multiple EGFR ligands participate in guiding migrating border cells. *Dev. Biol.* **296**, 94-103. doi:10.1016/j.ydbio.2006.04.438
Mongera, A., Rowghanian, P., Gustafson, H. J., Shelton, E., Kealhofer, D. A., Carn, E. K., Serwane, F., Lucio, A. A., Giammona, J. and Campas, O. (2018). A fluid-to-solid jamming transition underlies vertebrate body axis elongation. *Nature* **561**, 401. doi:10.1038/s41586-018-0479-2
Monier, B., Gettings, M., Gay, G., Mangeat, T., Schott, S., Guarner, A. and Suzanne, M. (2015). Apico-basal forces exerted by apoptotic cells drive epithelium folding. *Nature* **518**, U245-U252. doi:10.1038/nature14152
Niwayama, R., Shinohara, K. and Kimura, A. (2011). Hydrodynamic property of the cytoplasm is sufficient to mediate cytoplasmic streaming in the Caenorhabiditis elegans embryo. *Proc. Natl. Acad. Sci. USA* **108**, 11900-11905. doi:10.1073/pnas.1101853108
O'Neill, P. R., Castillo-Badillo, J. A., Meshik, X., Kalyanaraman, V., Melgarejo, K. and Gautam, N. (2018). Membrane flow drives an adhesion-independent amoeboid cell migration mode. *Dev. Cell* **46**, 9. doi:10.1016/j.devcel.2018.05.029
Paluch, E. K., Aspalter, I. M. and Sixt, M. (2016). Focal adhesion-independent cell migration. *Annu. Rev. Cell Dev. Biol.* **32**, 469-490. doi:10.1146/annurev-cellbio-111315-125341
Park, J. A., Atia, L., Mitchel, J. A., Fredberg, J. J. and Butler, J. P. (2016). Collective migration and cell jamming in asthma, cancer and development. *J. Cell Sci.* **129**, 3375-3383. doi:10.1242/jcs.187922
Poujade, M., Grasland-Mongrain, E., Hertzog, A., Jouanneau, J., Chavrier, P., Ladoux, B., Buguin, A. and Silberzan, P. (2007). Collective migration of an epithelial monolayer in response to a model wound. *Proc. Natl. Acad. Sci. USA* **104**, 15988-15993. doi:10.1073/pnas.0705062104
Poukkula, M., Cliffe, A., Changede, R. and Rørth, P. (2011). Cell behaviors regulated by guidance cues in collective migration of border cells. *J. Cell Biol.* **192**, 513-524. doi:10.1083/jcb.201010003
Prasad, M. and Montell, D. J. (2007). Cellular and molecular mechanisms of border cell migration analyzed using time-lapse live-cell Imaging. *Dev. Cell* **12**, 997-1005. doi:10.1016/j.devcel.2007.03.021
Rauzi, M., Lenne, P.-F. and Lecuit, T. (2010). Planar polarized actomyosin contractile flows control epithelial junction remodelling. *Nature* **468**, U1110-U515. doi:10.1038/nature09566
Reffay, M., Parrini, M. C., Cochet-Escartin, O., Ladoux, B., Buguin, A., Coscoy, S., Amblard, F., Camonis, J. and Silberzan, P. (2014). Interplay of RhoA and mechanical forces in collective cell migration driven by leader cells. *Nat. Cell Biol.* **16**, 217. doi:10.1038/ncb2917
Revenu, C., Streichan, S., Dona, E., Lecaudey, V., Hufnagel, L. and Gilmour, D. (2014). Quantitative cell polarity imaging defines leader-to-follower transitions during collective migration and the key role of microtubule-dependent adherens junction formation. *Development* **141**, 1282-1291. doi:10.1242/dev.101675
Ridley, A. J., Schwartz, M. A., Burridge, K., Firtel, R. A., Ginsberg, M. H., Borisy, G., Parsons, J. T. and Horwitz, A. R. (2003). Cell migration: Integrating signals from front to back. *Science* **302**, 1704-1709. doi:10.1126/science.1092053
Röper, K. (2013). Supracellular actomyosin assemblies during development. *Bioarchitecture* **3**, 45-49. doi:10.4161/bioa.25339
Rørth, P. (2012). Fellow travellers: emergent properties of collective cell migration. *EMBO Rep.* **13**, 984-991. doi:10.1038/embor.2012.149
Roycroft, A. and Mayor, R. (2016). Molecular basis of contact inhibition of locomotion. *Cell. Mol. Life Sci.* **73**, 1119-1130. doi:10.1007/s00018-015-2090-0
Roycroft, A., Szabo, A., Bahm, I., Daly, L., Charras, G., Parsons, M. and Mayor, R. (2018). Redistribution of adhesive forces through Src/FAK drives contact inhibition of locomotion in neural crest. *Dev. Cell* **45**, 565. doi:10.1016/j.devcel.2018.05.003
Rozbicki, E., Chuai, M., Karjalainen, A. I., Song, F. F., Sang, H. M., Martin, R., Knolker, H. J., MacDonald, M. P. and Weijer, C. J. (2015). Myosin-II-mediated

cell shape changes and cell intercalation contribute to primitive streak formation. *Nat. Cell Biol.* **17**, 397. doi:10.1038/ncb3138

Russo, J. M., Florian, P., Shen, L., Graham, W. V., Tretiakova, M. S., Gitter, A. H., Mrsny, R. J. and Turner, J. R. (2005). Distinct temporal-spatial roles for rho kinase and myosin light chain kinase in epithelial purse-string wound closure. *Gastroenterology* **128**, 987-1001. doi:10.1053/j.gastro.2005.01.004

Ruth, E. S. (1911). Cicatrization of wounds in vitro. *J. Exp. Med.* **13**, 422-424. doi:10.1084/jem.13.4.422

Sanchez-Corrales, Y. E. and Röper, K. (2018). Alignment of cytoskeletal structures across cell boundaries generates tissue cohesion during organ formation. *Curr. Opin. Cell Biol.* **55**, 104-110. doi:10.1016/j.ceb.2018.07.001

Scarpa, E., Szabó, A., Bibonne, A., Theveneau, E., Parsons, M. and Mayor, R. (2015). Cadherin switch during EMT in neural crest cells leads to contact inhibition of locomotion via repolarization of forces. *Dev. Cell* **34**, 421-434. doi:10.1016/j.devcel.2015.06.012

Sedgwick, A. (1894). On the inadequacy of the cellular theory of development, and on the early development of nerves, particularly of the third nerve and of the sympathetic in Elasmobranchii. *Quart. J. Micro. Sci.* **s2-37**, 87-101. http://jcs.biologists.org/content/s2-37/145/87

Serra-Picamal, X., Conte, V., Vincent, R., Anon, E., Tambe, D. T., Bazellieres, E., Butler, J. P., Fredberg, J. J. and Trepat, X. (2012). Mechanical waves during tissue expansion. *Nat. Phys.* **8**, U628-U66. doi:10.1038/nphys2355

Shannon, E. K., Stevens, A., Edrington, W., Zhao, Y. H., Jayasinghe, A. K., Page-McCaw, A. and Hutson, M. S. (2017). Multiple mechanisms drive calcium signal dynamics around laser-induced epithelial wounds. *Biophys. J.* **113**, 1623-1635. doi:10.1016/j.bpj.2017.07.022

Shellard, A. and Mayor, R. (2016). Chemotaxis during neural crest migration. *Semin. Cell Dev. Biol.* **55**, 111-118. doi:10.1016/j.semcdb.2016.01.031

Shellard, A., Szabo, A., Trepat, X. and Mayor, R. (2018). Supracellular contraction at the rear of neural crest cell groups drives collective chemotaxis. *Science* **362**, 339. doi:10.1126/science.aau3301

Shewan, A. M., Maddugoda, M., Kraemer, A., Stehbens, S. J., Verma, S., Kovacs, E. M. and Yap, A. S. (2005). Myosin 2 is a key Rho kinase target necessary for the local concentration of E-cadherin at cell-cell contacts. *Mol. Biol. Cell* **16**, 4531-4542. doi:10.1091/mbc.e05-04-0330

Siekmann, A. F. and Lawson, N. D. (2007). Notch signalling limits angiogenic cell behaviour in developing zebrafish arteries. *Nature* **445**, 781-784. doi:10.1038/nature05577

Simske, J. S. and Hardin, J. (2001). Getting into shape: epidermal morphogenesis in Caenorhabditis elegans embryos. *BioEssays* **23**, 12-23. doi:10.1002/1521-1878(200101)23:1<12::AID-BIES1003>3.0.CO;2-R

Smith, L. D. and Ecker, R. E. (1970). Uterine suppression of biochemical and morphogenetic events in rana-pipiens. *Dev. Biol.* **22**, 622. doi:10.1016/0012-1606(70)90172-7

Smutny, M., Akos, Z., Grigolon, S., Shamipour, S., Ruprecht, V., Capek, D., Behrndt, M., Papusheva, E., Tada, M., Hof, B. et al. (2017). Friction forces position the neural anlage. *Nat. Cell Biol.* **19**, 306. doi:10.1038/ncb3492

Solon, J., Kaya-Copur, A., Colombelli, J. and Brunner, D. (2009). Pulsed forces timed by a ratchet-like mechanism drive directed tissue movement during dorsal closure. *Cell* **137**, 1331-1342. doi:10.1016/j.cell.2009.03.050

Stevenson, C., Menegas, W., Zajac, A., Williams, A., Cheng, S., Ozkan, E. and Horne-Badovinac, S. (2019). Planar polarized Semaphorin-5c and Plexin A promote the collecive migration of epithelial cells in Drosophila. *Curr. Biol.* **29**, 908-920.e6 doi:10.1016/j.cub.2019.01.049

Stramer, B. and Mayor, R. (2017). Mechanisms and in vivo functions of contact inhibition of locomotion. *Nat. Rev. Mol. Cell Biol.* **18**, 43-55. doi:10.1038/nrm.2016.118

Sunyer, R., Conte, V., Escribano, J., Elosegui-Artola, A., Labernadie, A., Valon, L., Navajas, D., Garcia-Aznar, J. M., Munoz, J. J., Roca-Cusachs, P. et al. (2016). Collective cell durotaxis emerges from long-range intercellular force transmission. *Science* **353**, 1157-1161. doi:10.1126/science.aaf7119

Tambe, D. T., Hardin, C. C., Angelini, T. E., Rajendran, K., Park, C. Y., Serra-Picamal, X., Zhou, E. H., Zaman, M. H., Butler, J. P., Weitz, D. A. et al. (2011). Collective cell guidance by cooperative intercellular forces. *Nat. Mater.* **10**, 469-475. doi:10.1038/nmat3025

Tanaka, M., Kikuchi, T., Uno, H., Okita, K., Kitanishi-Yumura, T. and Yumura, S. (2017). Turnover and flow of the cell membrane for cell migration. *Sci. Rep.* **7**, 12970. doi:10.1038/s41598-017-13438-5

Theveneau, E., Marchant, L., Kuriyama, S., Gull, M., Moepps, B., Parsons, M. and Mayor, R. (2010). Collective chemotaxis requires contact-dependent cell polarity. *Dev. Cell* **19**, 39-53. doi:10.1016/j.devcel.2010.06.012

Tozluoglu, M., Tournier, A. L., Jenkins, R. P., Hooper, S., Bates, P. A. and Sahai, E. (2013). Matrix geometry determines optimal cancer cell migration strategy and modulates response to interventions. *Nat. Cell Biol.* **15**, 751. doi;10.1038/ncb2775

Trepat, X., Wasserman, M. R., Angelini, T. E., Millet, E., Weitz, D. A., Butler, J. P. and Fredberg, J. J. (2009). Physical forces during collective cell migration. *Nat. Phys.* **5**, 426-430. doi:10.1038/nphys1269

Uhlenhuth, E. (1914). Cultivation of the skin epithelium of the adult frog, Rana pipiens. *J. Exp. Med.* **20**, 614-635. doi:10.1084/jem.20.6.614

Valentin, G., Haas, P. and Gilmour, D. (2007). The chemokine SDF1a coordinates tissue migration through the spatially restricted activation of Cxcr7 and Cxcr4b. *Curr. Biol.* **17**, 1026-1031. doi:10.1016/j.cub.2007.05.020

van Helvert, S., Storm, C. and Friedl, P. (2018). Mechanoreciprocity in cell migration. *Nat. Cell Biol.* **20**, 8-20. doi:10.1038/s41556-017-0012-0

Vedula, S. R. K., Leong, M. C., Lai, T. L., Hersen, P., Kabla, A. J., Lim, C. T. and Ladoux, B. (2012). Emerging modes of collective cell migration induced by geometrical constraints. *Proc. Natl. Acad. Sci. USA* **109**, 12974-12979. doi:10.1073/pnas.1119313109

Vedula, S. R. K., Hirata, H., Nai, M. H., Brugués, A., Toyama, Y., Trepat, X., Lim, C. T. and Ladoux, B. (2014). Epithelial bridges maintain tissue integrity during collective cell migration. *Nat. Mater.* **13**, 87-96. doi:10.1038/nmat3814

Venkiteswaran, G., Lewellis, S. W., Wang, J., Reynolds, E., Nicholson, C. and Knaut, H. (2013). Generation and dynamics of an endogenous, self-generated signaling gradient across a migrating tissue. *Cell* **155**, 674-687. doi:10.1016/j.cell.2013.09.046

Verger, S., Long, Y. C., Boudaoud, A. and Hamant, O. (2018). A tension-adhesion feedback loop in plant epidermis. *Elife* **7**, e34460. doi:10.7554/eLife.34460

Viktorinova, I. and Dahmann, C. (2013). Microtubule polarity predicts direction of egg chamber rotation in Drosophila. *Curr. Biol.* **23**, 1472-1477. doi:10.1016/j.cub.2013.06.014

Viktorinova, I., Konig, T., Schlichting, K. and Dahmann, C. (2009). The cadherin Fat2 is required for planar cell polarity in the Drosophila ovary. *Development* **136**, 4123-4132. doi:10.1242/dev.039099

Vishwakarma, M., Di Russo, J., Probst, D., Schwarz, U. S., Das, T. and Spatz, J. P. (2018). Mechanical interactions among followers determine the emergence of leaders in migrating epithelial cell collectives. *Nat. Commun.* **9**, 3469. doi:10.1038/s41467-018-05927-6

Vogt, W. (1923). Morphologische und physiologische Fragen der Primitiventwicklung. *Sitz. Ber. d. Ges. f. Morph. u. Physiol. Miinchen* **35**, 22.

Voiculescu, O., Bertocchini, F., Wolpert, L., Keller, R. E. and Stern, C. D. (2007). The amniote primitive streak is defined by epithelial cell intercalation before gastrulation. *Nature* **449**, 1049-1052. doi:10.1038/nature06211

Voituriez, R., Joanny, J. F. and Prost, J. (2006). Generic phase diagram of active polar films. *Phys. Rev. Lett.* **96**. doi:10.1103/PhysRevLett.96.028102

Wan, P., Wang, D., Luo, J., Chu, D. D., Wang, H., Zhang, L. J. and Chen, J. (2013). Guidance receptor promotes the asymmetric distribution of exocyst and recycling endosome during collective cell migration. *Development* **140**, 4797-4806. doi:10.1242/dev.094979

Wang, X. B., He, L., Wu, Y. I., Hahn, K. M. and Montell, D. J. (2010). Light-mediated activation reveals a key role for Rac in collective guidance of cell movement in vivo. *Nat. Cell Biol.* **12**, U591-U154. doi:10.1038/ncb2061

Wang, X., Enomoto, A., Weng, L., Mizutani, Y., Abudureyimu, S., Esaki, N., Tsuyuki, Y., Chen, C., Mii, S., Asai, N. et al. (2018). Girdin/GIV regulates collective cancer cell migration by controlling cell adhesion and cytoskeletal organization. *Cancer Sci.* **109**, 3643-3656. doi:10.1111/cas.13795

Weber, G. F., Bjerke, M. A. and DeSimone, D. W. (2011). Integrins and cadherins join forces to form adhesive networks. *J. Cell Sci.* **124**, 1183-1193. doi:10.1242/jcs.064618

Weber, G. F., Bjerke, M. A. and DeSimone, D. W. (2012). A mechanoresponsive cadherin-keratin complex directs polarized protrusive behavior and collective cell migration. *Dev. Cell* **22**, 104-115. doi:10.1016/j.devcel.2011.10.013

Wen, J. W. H. and Winklbauer, R. (2017). Ingression-type cell migration drives vegetal endoderm internalisation in the Xenopus gastrula. *Elife* **6**, e27190. doi:10.7554/eLife.27190

Whitman, C. O. (1893). The inadequacy of the cell-theory of development. *J. Morphol.* **8**, 639-658. doi:10.1002/jmor.1050080307

Wood, W., Jacinto, A., Grose, R., Woolner, S., Gale, J., Wilson, C. and Martin, P. (2002). Wound healing recapitulates morphogenesis in Drosophila embryos. *Nat. Cell Biol.* **4**, 907-912. doi:10.1038/ncb875

Yao, M. X., Qiu, W., Liu, R. C., Efremov, A. K., Cong, P. W., Seddiki, R., Payre, M., Lim, C. T., Ladoux, B., Mege, R. M. et al. (2014). Force-dependent conformational switch of alpha-catenin controls vinculin binding. *Nat. Commun.* **5**, 4525. doi:10.1038/ncomms5525

Yonemura, S., Wada, Y., Watanabe, T., Nagafuchi, A. and Shibata, M. (2010). alpha-Catenin as a tension transducer that induces adherens junction development. *Nat. Cell Biol.* **12**, 533-542. doi:10.1038/ncb2055

Yoon, J., Hwang, Y. S., Lee, M., Sun, J., Cho, H. J., Knapik, L. and Daar, I. O. (2018). TBC1d24-ephrinB2 interaction regulates contact inhibition of locomotion in neural crest cell migration. *Nat. Commun.* **9**, 3491. doi:10.1038/s41467-018-05924-9

Zulueta-Coarasa, T. and Fernandez-Gonzalez, R. (2018). Dynamic force patterns promote collective cell movements during embryonic wound repair. *Nat. Phys.* **14**, 750. doi:10.1038/s41567-018-0111-2