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Review

Interplay between intercellular signaling and cell movement in development

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ABSTRACT

Cell movement and local intercellular signaling are crucial components of morphogenesis during animal development. Intercellular signaling regulates the collective movement of a cell population via direct cell–cell contact. Cell movement, conversely, can influence local intercellular signaling by rearranging neighboring cells. Here, we first discuss theoretical models that address how intercellular signaling regulates collective cell movement during development. Examples include neural crest cell migration, convergent extension, and cell movement during vertebrate axis elongation. Second, we review theoretical studies on how cell movement may affect intercellular signaling, using the segmentation clock in zebrafish as an example. We propose that interplay between cell movement and intercellular signaling must be considered when studying morphogenesis in embryonic development.

Contents

1. Introduction

Cell movement is essential for morphogenesis during embryonic development. Remarkably, cell movement direction can be highly correlated among cells in a group such that they collectively move toward a destination. This is known as collective cell movement. Examples of collective cell movement include neural crest migration toward specific embryonic locations, mesendoderm migration from the germ ring margin toward the animal pole, lateral line primordium in zebrafish, axis elongation by convergent extension, and branching in lung and blood vessel development [1,2]. How collective cell movement occurs is relevant to understanding many morphological processes.

To collectively move in the correct direction, cells need mechanisms to organize their behavior across the population. Directional cues, for example, could be provided by a long distance signaling gradient. Cells themselves may tightly adhere to each other via adhesion molecules to form a solid group, such as mesendoderm cells, or remain loosely associated, such as neural crest cells. Intercellular signaling plays an important role in both cases to maintain coherent cellular movement (Fig. 1A). Signals can be transmitted

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Fig. 1. Interplay between intercellular signaling and cell movement. (A) Signaling affects movement. (B) Movement affects signaling. (C) Feedback loop between cell movement and intercellular signaling.

across a population of cells through mechanical force or biochemical reactions.

Experiments have revealed key molecules regulating intercellular signaling during collective cell movement. These molecules include cell adhesion molecules, such as cadherin, as well as members of the Wnt/planar cell polarity (PCP) signaling pathway and intracellular actomyosin networks. How intercellular signaling mediated by these molecules gives rise to collective cell movement awaits future investigation. Theoretical modeling will aid this investigation by suggesting underlying physical mechanisms that emerge from the orchestration of different signaling pathways [3].

Much is known about how intercellular signaling controls cell movement in embryonic development, but what about the converse? Does cell movement influence intercellular signaling? If cells use short-range intercellular interactions, the network topology of intercellular interactions, i.e. which cells interact, strongly determines the information flow across a cell population. Cell movement dynamically rearranges neighboring cells, which changes the network topology over time. If the timescale of cell movement is much slower than intercellular signaling, the effect of changing relative cell positions on signaling would be negligible. However, if the time scale of cell movement is comparable to the timescale of intercellular signaling, cell movement may affect intercellular signaling (Fig. 1B).

Here, we discuss how intercellular signaling regulates cell movement with three examples from embryonic development. We introduce theoretical models of collective cell movement regulated by intercellular signaling. Lastly, we discuss how cell movement influences intercellular signaling, with an example from vertebrate somitogenesis. We propose that consideration of the interplay between intercellular signaling and cell movement is essential to understand embryonic morphogenesis (Fig. 1C). Theoretical modeling will be a powerful tool, combined with quantitative experiments, to elucidate the effects of this interplay during morphogenesis.

2. Signaling affects movement

2.1. Collective neural crest migration

Neural crest cells are induced in a vertebrate embryonic tissue called the neural plate border, a boundary between the neuroectoderm and the nonneural ectoderm in the neural tube. After they migrate into their final destination, neural crest cells differentiate into a broad range of cell types, such as neurons, glia, medullary secretory cells, smooth muscle cells, melanocytes, bone and cartilage cells [4,5]. The induction of neural crest cells involves complex gene-regulatory networks including Wnt, bone morphogenetic proteins (BMPs), and fibroblast growth factor (FGF) signaling (see reviews [4,6,7]). Undergoing an epithelial to mesenchymal transition, neural crest cells delaminate from the neuroepithelium then migrate long distances (on the order of millimeters) toward their destinations along stereotypical routes in the embryo. Remarkably, neural crest cells migrate as a coherent group. Theoretical studies have been addressing how migrating neural crest cells form and maintain their collective movement.

Biologists have been trying to understand mechanisms by which neural crest cells determine their final destinations. One simple answer to this question would be that neural crest cells sense a signaling gradient from their destination, and follow this long-range signal. Indeed, several chemoattractants, such as stromal-cell-derived factor 1, vascular endothelial growth factor, platelet-derived growth factor and FGF have been found along the routes on which neural crest cells migrate [4,8,9].

Interestingly, neural crest cells internalize and consume chemoattractants on their migration routes. This raises the question of how neural crest cells that emerge later from the neural tube can migrate correctly, because the chemoattractant would have been internalized and consumed by neural crest cells migrating earlier. Using theoretical modeling, McLennan et al. explored the situation in which later emigrating neural crest cells cannot sense the signaling gradient because of its low concentration, and showed that if these cells do not have other mechanisms to find their destinations, they stay near their exit site from the neural tube [10]. This suggests the existence of a mechanism that allows later emigrating neural crest cells to follow earlier emigrating neural crest cells without a signaling gradient.

McLennan et al. proposed that the observed long-distance migration of a neural crest cell group can be explained if there are two different types of neural crest cells (Fig. 2A: [10]). One is the "leading cell" that emerges earlier from the neural tube and follows an intact chemoattractant on its migration routes. The other cell type is a "trailing cell" that emerges later and does not follow the signaling gradient, but tries to attach to a leader cell. Trailing cells can attach to a trailing cell that already attaches to a leader cell. Thus, a chain of trailing cells can form behind a leader cell.

McLennan et al. experimentally tested the prediction of this theory by examining the gene expression profiles in early and late emigrating neural crest cells [10]. The experiment revealed that leading cells upregulate different sets of genes from trailing cells. In leading cells, these upregulated genes include cell guidance factor receptors (e.g. EphA4), integrins, matrix metalloproteases and cadherins. In contrast, trailing cells express cadherins different from leading cells. Further transplantation experiments supported the hypothesis that the existence of two different types of neural crest cells is vital for their migration. Thus, theory and experiment suggest a mechanism by which a group of neural crest cells migrate long distances together. Forming a group ensures the coherent long-distance migration of early and late appearing neural crest cells.

Recently, a cell-automaton model that includes both leading and trailing cells revealed conditions for generating a persistent chain of neural crest cells [11]. Wynn et al. carried out an extensive sensitivity analysis for parameters in their cell-automaton model. Their analysis predicted that the chain is more persistent when leading cells frequently change the direction of their filopodia to search for trailing cells, and move toward trailing cells once they are found. In contrast, trailing cells that do not frequently change their direction of movement enhance chain formation. Detailed comparisons of these two cell type behaviors with live imaging will be able to test the prediction of this model in the future.

Another important observation of neural crest migration is that neural crest cells form coherent migrating groups even without tight physical junctions between them. For this, short-range intermittent interactions among migrating cells should play key roles. Currently, two different signaling mechanisms, contact inhibition of locomotion (CIL: Fig. 2B) and coattraction (Fig. 2C), have been reported in neural crest cells.

CIL was first identified 60 years ago in chick fibroblasts [12]. Neural crest cells also exhibit CIL in vivo and in vitro during

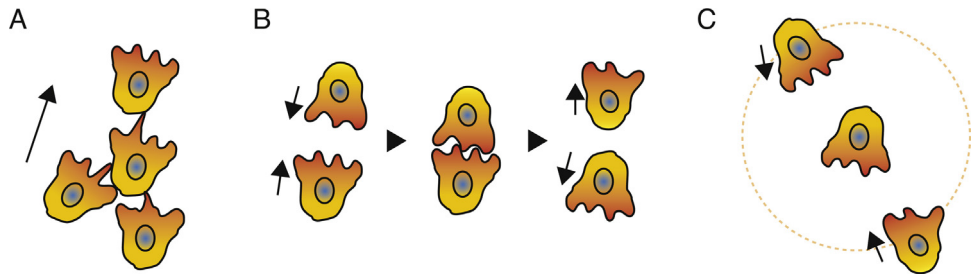

Fig. 2. Collective neural crest cell migration. (A) Leading and trailing neural crest cells for long-distance migration. The arrow indicates the direction of motion of the chain. (B) Contact inhibition of locomotion. (C) Local attraction by chemoattractant C3.

migration [13]. When two neural crest cells physically touch each other, their touching cellular protrusions tend to collapse, and they form new protrusions at the opposite sides of the touching point. Subsequently, the cells change the direction of motion and tend to move away from each other. CIL occurs only when neural crest cells make contact with each other [13]; if a neural crest cell contacts a cell of different type, such as a mesoderm cell, it does not show CIL.

In *Xenopus*, CIL depends on the non-canonical Wnt pathway [13]. Dishevelled localizes to the contact surface of two touching neural crest cells before the cells change their directions of motion. Dishevelled, in turn, activates RhoA on the contact surface. Local RhoA activation at the contact surface leads to the collapse of cellular protrusions and to the change in the direction of cellular motion.

An interesting theoretical question is what types of migration patterns CIL alone can cause in a cell population. Recently, a physical model for CIL was developed to explain a spatial distribution pattern of *Drosophila* macrophages [14]. The model describes the persistent random walk of macrophages with repulsive interactions among them as CIL in a confined domain. Numerical simulations demonstrated that this CIL model can quantitatively reproduce the dispersed spatial distribution of macrophages in the ventral surface of *Drosophila*.

However, it can be expected that neural crest cells disperse during their migration period if they interact with each other only using CIL. Carmona-Fontaine et al. showed by an agent-based model that a population of neural crest cells cannot form a cohesive migrating group, but simply disperse under CIL [15]. The model predicted that neural crest cells would require a short-range attraction mechanism among neighboring cells to balance the dispersing effect of CIL and to form a cohesive migrating group.

The prediction of this agent-based model motivated experimentalists to search for candidate molecules to mediate this attraction mechanism among neural crest cells. A detailed search for secreted proteins in in situ hybridization databases revealed C3, a key component of the complement pathway, as a candidate for the chemoattractant [15]. Subsequent experiments indicate that C3 and its receptor C3ar are produced in migrating neural crest cells, and indeed C3 is a chemoattractant of these cells [15].

Thus, migrating neural crest cells use two types of short-range signaling: a repulsive interaction by CIL (Fig. 2B), and an attractive interaction by C3 (Fig. 2C). But why do neural crest cells need these two opposing intercellular signaling processes? Carmona-Fontaine et al. pointed out that the answer to this question might be found in studies on the collective migration of animal groups where similar short-range interactions, both repulsion and attraction between individuals, are known as a mechanism for collective migration [15,16]. These studies consider the predatory behavior of animals; an individual tries to pursue other individuals moving in its front (i.e. attracted), while the individual tries to escape if approached from behind by another individual (i.e. repulsive). Numerical simulations demonstrated that a population of these interacting animals exhibits collective migration [16]. Similarly, having balanced attracting and repulsive interactions might cause the collective movement of neural crest cells.

We have reviewed mechanisms for long distance migration of neural crest cells and for forming a cohesive cellular group. In these cases, theoretical modeling played a key role for elucidating mechanisms and provoking the search for important molecules. In the future, theoretical models integrating both long- and short-range signaling for neural crest cell migration promise to reveal a more complete picture of their migratory behaviors. These models may connect fragmented experimental data with a small number of underlying mechanisms.

2.2. Cell intercalation in convergent extension

Embryos extend their anterior–posterior (AP) body axis during development. Mechanisms for axis elongation include oriented cell divisions, and cell shape changes [17,18]. Interestingly, cell movement also contributes to the axis elongation of embryos. One example is convergent extension (CE), which features the dynamic rearrangement of neighboring cells in a tissue (Fig. 3).

Germ band elongation of the *Drosophila* along the AP axis of the embryo is an example of a CE mechanism where an epithelial tissue undergoes cell intercalation (Fig. 3A: [19]). Epithelial cells in this tissue dynamically rearrange their neighbors over time by junction remodeling and intercalate along the dorsal–ventral (DV) axis. Cell edges parallel to the DV axis gradually contract and they are replaced by a cell–cell contact parallel to the AP axis of other two cells.

The contraction of cell edges along DV axis occurs due to polarized accumulation of mysosinII in these cell edges (Fig. 3A), which increases the tension of those edges. Rauzi et al. investigated this problem using a theoretical model in which the contraction of cell edges induced by myosinII can cause cell intercalation and CE movement as observed in *Drosophila* germ band elongation [20]. They used a two-dimensional vertex dynamics model that describes a single cell by a polygon. Vertices of polygons move to realize a configuration that minimizes a potential function for the equation of motion. The vertex model has the advantage of being able to represent the contractility of cell edges by tensions between vertices. Rauzi et al. assumed the stronger contraction of cell edges perpendicular to the elongation axis in the potential function for the equation of motion. The authors explained that this anisotropic contraction of cell edges is induced by the accumulation of myosinII observed in *Drosophila*. They demonstrated that a vertex model including this anisotropic contraction can reproduce CE and the elongation rate observed in vivo. By using laser dissection in living tissues, Rauzi et al. confirmed the anisotropic tension of cell edges in single cells experimentally.

Convergent extension movements are also observed during zebrafish and *Xenopus* gastrulation, taking place in a more complex three-dimensional context than the epithelial sheet of the early *Drosophila* blastoderm discussed above. Progenitor cells first

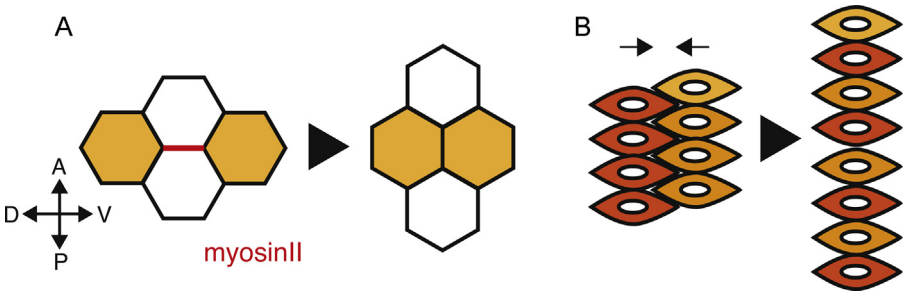

Fig. 3. Convergent extension. (A) Cell intercalation in *Drosophila* germ band elongation. The red line indicates the accumulation of myosinII. A: anterior, P: posterior, D: dorsal, and V: ventral. (B) Cell intercalation in *Xenopus* and zebrafish.

polarize and elongate along the medial–lateral axis perpendicular to the AP extension axis of the tissue (Fig. 3B: [21–23]). The polarized cells move collectively in the medial direction intercalating with their neighbors as they do. As a result, the width of the tissue along the medial–lateral axis is reduced, while the length of the tissue along the AP axis is extended. Similar CE movements seem to underlie notochord formation [24] and head fold formation in chick embryos [25]. Importantly, defects in CE cause impaired body axis elongation.

Experimental studies have revealed key signaling molecules responsible for orchestrating CE. In both *Xenopus* and zebrafish, the Wnt/PCP signaling pathway regulates cellular elongation and polarization required for CE movement [23]. Molecular components of the PCP pathway are polarized in elongated cells. For example, in *Xenopus* CE, Dishevelled accumulates at the medial tip of mediolaterally elongated cells. PCP signaling also regulates the assembly of extracellular matrix, especially fibronectin and fibrillin [26]. In the zebrafish gastrula, BMP signaling restricts the domains where CE occurs. A BMP signal forms a gradient along the DV axis, higher in the ventral region of the embryo. BMP negatively regulates Wnt11 and Wnt5a, suppressing CE in the ventral region [27]. Moreover, BMP signaling controls the direction of cell movement in CE by negatively regulating N-cadherin activity in lamellipodial cellular protrusions [28]. Thus, the BMP gradient generates an opposing gradient of N-cadherin along the DV axis. It is thought that cells tend to move in the direction of higher N-cadherin activity, because they can form more stable cell–cell contacts used for displacement.

It has been known from classical embryology that isolated tissue explanted from the *Xenopus* gastrula could undergo CE without external forces, indicating that CE is a tissue-autonomous process [29]. Since then, several theoretical models have addressed the mechanism by which a tissue produces CE as its emergent property.

Zajac et al. proposed that the minimization of intercellular adherence energy alone can induce cell alignment and intercalation similar to that observed in CE [30,31]. The authors considered a population of elongated cells and assumed an anisotropy of adherence energy among contact surfaces; (1) cell–cell adhesion is strongest when two neighboring cells contact with their longer sides, and (2) adhesion between the shorter-sides of two cells is stronger than adhesion between a longer side of one cell and a shorter side of the other. The authors implemented this anisotropic differential adhesion with a cellular Potts model [31]. The cellular Potts model describes individual cells as a cluster of lattice sites in a two dimensional lattice space. It is suited for representation of anisotropic cellular shapes and modeling cell adhesion. Zajac et al. reproduced CE movement in simulations of the cellular Potts model with anisotropic differential adhesion [31]. Although molecules responsible for anisotropic differential adhesion have not been identified, the involvement of cell adhesion molecules such as Cadherin in CE has been reported, as described above.

Honda et al. examined a mechanism termed cell shuffling [32], which assumes two phases of cellular behaviors, extension and relaxation. In the extension phase, cells synchronously elongate in the direction perpendicular to the tissue extension axis. In the relaxation phase, cells contract their elongated edges to recover their natural perimeter. Honda et al. assumed that these two phases occur periodically. The authors developed a three-dimensional vertex dynamics model where a single cell is represented as a polyhedron, and they computed the equation of motion for each vertex of the polyhedrons. The authors demonstrated that periodic transition between the extension and relaxation phases in the model can induce cell intercalation and similar CE in embryos.

Brodland studied the effects of tension caused by lamellipodia on cell shape and intercalation in CE [33]. The author used a two-dimensional finite element model where single cells are represented as polygons. Tension along each cell–cell interface and the viscosity of cytoplasm change the positions of the vertices of polygons. Brodland assumed that cells tend to extend lamellipodia along the axis perpendicular to the tissue extension axis. A lamellipodium from a cell attaches to a second nearest neighbor cell, and the lamellipodium pulls the attached cell. Brodland demonstrated by numerical simulation that the tension mediated by lamellipodia induces intercalation of these two cells. The author also pointed out that elongated cell shapes appear in simulations only when the lateral boundaries of a converging tissue is fixed by the surrounding tissues. This last prediction was successfully tested experimentally [33].

For *Drosophila* germ band elongation, good progress has been made by the combination of theory and experiment in understanding the driving force of CE. In contrast, it seems that there are still gaps between theory and experiment for understanding CE movement in *Xenopus* and zebrafish embryos. Simultaneous observation of cellular behaviors and molecular distributions within single cells by time lapse imaging, together with corresponding theoretical modeling should help to reveal the major driving force(s) of CE movements in these embryos.

2.3. Cell movement during vertebrate posterior axis elongation

In the previous section, we have seen the importance of CE for axis elongation in early embryos. After gastrulation, CE also occurs in the anterior presomitic mesoderm (PSM) and contributes to vertebrate elongation [34]. In this section, we discuss another type of cell movement occurring in the posterior PSM and tailbud that appears to underlie posterior axis elongation in vertebrate embryos at later stages.

It has been proposed that cell movement in the posterior PSM is crucial for proper axis elongation in chick and zebrafish embryos (Fig. 4: [35,36]). Bénazéraf et al. analyzed cell movement in the posterior chick PSM with high-resolution time-lapse imaging. The authors observed a gradient of cellular mobility along the AP axis of the PSM, as reported in previous studies [37,38] where cells in the

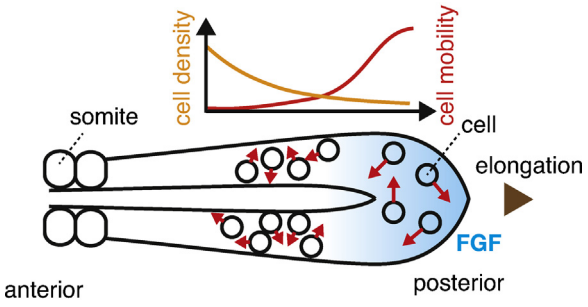

Fig. 4. Cell movement during vertebrate axis elongation. Red arrows indicate velocity of movement. The length of arrows represents speed.

posterior PSM are more mobile than anterior cells (Fig. 4), performing a random walk [35]. The mean squared displacement calculated from the trajectories of these cells increased linearly over time, which is a signature of diffusive cell movement. In addition, the direction of cell protrusions representing the direction of cellular motion was randomly distributed among cells.

Cell movement in the PSM is regulated by an FGF signaling gradient where the FGF signal is higher in posterior regions (Fig. 4: [35–37]). Bénazéraf et al. inhibited FGF signaling by a dominant negative form of FGF receptor, and found decreased cellular mobility in the posterior PSM. The authors also observed that the axis elongation rate decreased after FGF inhibition. To examine whether slower cell movement resulted in slower axis elongation, the authors directly inhibited cell movement with drugs inhibiting Rho kinase and myosinII phosphorylation. The inhibition of cell movement by these drugs induced slower axis elongation similar to FGF inhibition. Bénazéraf et al. concluded that cell movement in the chick PSM plays a crucial role in axis elongation.

How does this cell movement cause axis elongation in chick embryos? Bénazéraf et al. found that there is a gradient of cell density along the AP axis of the PSM (Fig. 4), opposing the gradient of cellular mobility [35]. Cell density is higher in anterior region than posterior. The authors speculate that this gradient of cell density plays a role in axis elongation by creating a directional bias in elongation. To relate the gradient of cell movement and that of cell density, the authors developed a stochastic individual-based model. They considered a population of cells randomly moving on a two-dimensional rectangular lattice. They assumed that cells tend to move from a site with higher cell density to a site with lower density. They also imposed an FGF signaling gradient along the longer side of the lattice. Cells in a site with higher FGF signal move with higher probability to a neighboring site. The model demonstrated that density dependent cell movement under FGF gradient can cause the gradient of cell density along the lattice. From these results, Bénazéraf et al. interpreted that the changes in cellular mobility could induce change in the axis elongation rate observed experimentally.

Recently, Lawton et al. measured a cell flow field in the zebrafish tailbud to study the effect of cell movement on posterior body axis elongation [36]. They divided the tailbud into three regions based on gene expression patterns and tissue morphology. In the dorsal medial zone located on a dorsal side of the tailbud, cell movement is ballistic and rapid. The direction of motions is strongly aligned among cells and they tend to keep their relative position. These cells coherently migrate into the progenitor zone, which is ventral to the dorsal medial zone and posterior to the notochord. Cells lose coherent movement in this region, and dynamically change their relative positions. Finally, cells flow into the PSM, and lose their mobility.

Lawton et al. studied signaling pathways that regulate the movement patterns observed in the zebrafish tailbud. The authors found that the inhibition of canonical Wnt, FGF, and cadherin2 significantly reduces the coherence of direction of motions across cells in the dorsal medial zone. The authors also observed axis elongation defects in embryos where these signaling pathways were inhibited. Particularly, a cell aggregation appearing as a bump was formed in the dorsal tailbud after Wnt inhibition.

To explain the formation of this cell aggregation, Lawton et al. used a physical model, originally proposed for collective movement of keratocytes [39], to describe the dynamics of velocity alignment of cells in the zebrafish tailbud. In the model, the authors assume that cells in the tailbud align their polarity for movement along the net force they receive from surrounding cells and the tissue boundaries. Lawton et al. argued that cells in the tailbud tend to change their direction of motions more frequently under Wnt inhibition than in wild type. They demonstrated in simulations that this highly fluctuating motion causes a jam of a cell flow in the dorsal medial zone. Due to the jam, cell density increases locally at this jammed region. The authors claimed that elevated cell density in the dorsal medial zone emerges as a cell aggregation in embryos under Wnt inhibition.

Thus, cell movement in the PSM and tailbud has been modeled in various ways to investigate its potential relevance to axis elongation. The next step would be to develop a physical model including related signaling pathways, cell movement and axis elongation, and simulate interplays among the processes. Experimental measurement of the distribution of physical forces generated by cell movement will be an important requirement to constrain a physical model.

3. Movement affects signaling

3.1. Cell movement and synchronization of the segmentation clock

In previous sections, we have discussed how intercellular signaling affects cell movement. Now we move to the reciprocal process: how cell movement affects intercellular signaling (Fig. 1B). Cell movement can cause the dynamic rearrangement of neighboring cells (Fig. 5A). If cells interact only with their neighboring cells, for example through membrane-bound proteins, the rearrangement of neighboring cells might affect collective cellular behaviors arising from intercellular signaling. Zebrafish somitogenesis may provide an example where cellular movement influences collective cellular behaviors.

Somites are the embryonic precursors of segmental structures in the adult body, such as vertebrae. During vertebrate development, somites bud off sequentially from the anterior of the PSM (see reviews [40,41]). The segregation of somites occurs rhythmically about every 30 min in zebrafish embryos. Cells in the PSM have a genetic oscillator composed of negative feedback loops. It is likely that the somitogenesis period is determined by the oscillating gene expression observed in the PSM [42]. During somitogenesis, cells in the PSM interact with their neighboring cells with Delta and Notch trans-membrane proteins. Binding of Delta to Notch induces cleavage of Notch intercellular domain that activates oscillatory genes after transport into the nucleus. In zebrafish, the oscillating genes regulate the production of deltaC mRNA, making the amount of Delta proteins oscillate. By using this oscillatory intercellular signal, each cell in the PSM sends the information of its phase of oscillation to its neighbors. Therefore, cells can synchronize oscillation of gene expression between neighboring cells. In particular, the cell population in the tailbud shows tissue-level synchronization. The synchronization of cyclic gene expression among neighboring cells is indispensable to make proper somites.

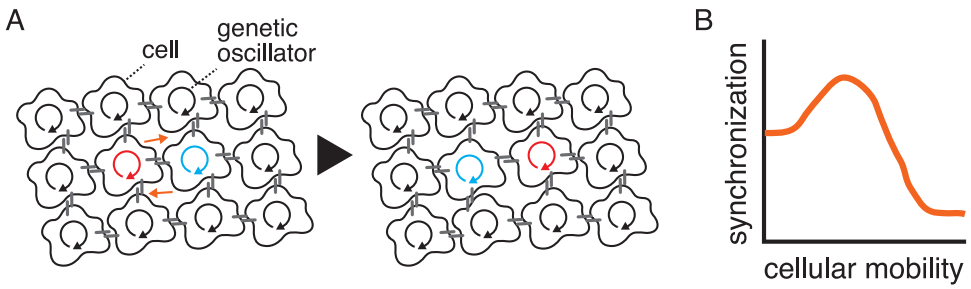

Fig. 5. Cell movement and synchronization of the segmentation clock. (A) Cell movement changes relative positions of cells. (B) Dependence of synchronization on cellular mobility.

Live imaging revealed that the cells in the tailbud move around during somitogenesis [35–38], as we described above. The reported cellular velocity seems to be comparable to the timescale of gene expression in zebrafish, meaning that cells would continually make and break Delta-Notch signaling contacts with their neighbors [43]. This raises the question of how cell movement might affect synchronization of coupled genetic oscillators across the cell population in the tissue.

The answer emerging from theoretical studies is that cell movement can enhance the synchronization of cyclic gene expression across the tailbud [43,44]. This prediction is supported by a theory of mobile coupled phase oscillators where each oscillator is described by a single variable, a phase describing the state of the oscillator in the cycle [45–48]. These theoretical studies compared the synchronization dynamics of mobile and non-mobile coupled oscillators.

Uriu et al. modeled the tailbud of zebrafish as a two-dimensional lattice, across which the phase of cyclic gene expression is uniformly synchronized [44]. To study the effects of cell movement on synchronization, the authors observed how a cell population attained synchronization across the lattice from random initial phases. Non-mobile cells tend to form local synchronization clusters, appearing as a spatially non-uniform phase pattern, rather than attaining uniform synchronization across a domain [44,46]. This is because a non-mobile cell with a local coupling through membrane proteins cannot see the phase of distant cells. These spatial phase patterns are persistent and prevent a population from reaching uniform synchronization across the domain. Thus, a population of non-mobile cells easily forms local phase order, but it struggles to attain global phase order.

In contrast, mobile cells can destabilize these spatial phase patterns by introducing phase mismatches among new local neighbors. Moreover, mobility provides cells with chances to interact with initially distant cells. A recent theoretical study of mobile identical phase oscillators revealed that the interaction range of each oscillator effectively extends as the square root of the mobility rate [48]. Thus, the theory suggests that cellular mobility enhances information spreading by extending the interaction range of cells.

These theoretical studies predict that cells moving faster achieve synchronization faster. An important assumption of these studies is that an oscillator can interact with its new neighbors with full capacity immediately after movement. However, in reality, these cells communicate with each other through membrane proteins, which necessitates interaction of ligands and receptors on the cellular surface to build communication channels with new neighboring cells. This takes time, and implies that cells moving faster than they can make strong communication channels will lose all interaction with neighboring cells.

A model including a more realistic gradual recovery of intercellular interactions after movement demonstrated that there is an optimal cellular mobility for synchronization (Fig. 5B: [43]). Cells moving at this optimal rate attain synchronization faster and more strongly. As we described above, cell movement effectively extends the interaction range of cells. However, if they move too fast, they cannot recover intercellular interactions. The appearance of this optimal mobility is the consequence of the competition of two time scales: the one for cell movement and the other for signaling recovery.

Thus, theoretical studies predict a significant impact of cell movement on the outcome of intercellular signaling. A missing piece is to test the theory in living tissues. Recently, live reporters of cyclic gene expression in zebrafish PSM were used to estimate the phase of oscillation at single cell level [49] (for the segmentation clock in other animals, see [50]). Cellular mobility in the PSM has been extensively measured [35,36], as we discussed above. Combining these experimental techniques, the prediction from the theory will be tested in the future.

The example of the segmentation clock suggests more generally that changes in relative cell positions induced by cell movement will affect intercellular signaling if the timescale of cell movement and that of signaling are similar. In the previous sections, we discussed neural crest cell migration and CE as the examples of how signaling affects cell movement. In neural crest cell migration and CE, however, the rearrangement of neighboring cells also occurs simultaneously with intercellular signaling. This raises the possibility that cell movement might affect signaling in both neural crest cell migration and CE.

4. Conclusion

We have reviewed theoretical studies on how signaling affects cell movement and how cell movement affects signaling during embryonic development. Many of these studies were done in close collaboration with experiments. Our consideration of current data leads to the proposal that a feedback loop exists between cell movement and intercellular signaling (Fig. 1C). Such feedback loops might be a general component of morphogenesis. Recently, Howard et al. revisited Alan Turing's ideas on morphogenesis [51], focusing on the interplay between biochemical and mechanical processes at the molecular and cellular scale [52]. Our proposal highlights a possible analogous feedback between information transfer and cellular movement at the tissue level. In both cases, the timescale determines whether the interplay is relevant. Large differences in timescales means these events can be analyzed independently, but if timescales are similar, then a feedback loop may be integral to the dynamics. Theoretical modeling will aid the description of collective cellular behaviors arising from interplay between cell movement and intercellular signaling. Advances in live imaging that enable simultaneous measurement of cell movement and intercellular signaling are key to testing theory.

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