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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.

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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

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