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Collective Cell Migration: Wisdom of the Crowds Transforms a Negative Cue into a Positive One

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https://doi.org/10.1016/j.cub.2019.02.001

The Semaphorin ligands and their Plexin receptors are known to induce cell–cell repulsion. A new study now finds that protrusion collapse, induced by Semaphorin-5C–Plexin-A interactions at the cell–cell contact, promotes planar polarization and collective migration of follicular cells in *Drosophila*.

A murmuration of starlings is a wonderful sight, a large mass of thousands of birds whirling in the sky above. This behaviour found in starlings is not unusual in nature and corresponds to a more general form of movement called collective migration, which has been studied extensively in animals, such as insect swarms, fish schools and flocks of birds like starlings [1]. Curiously, similar collective behaviour has been found at a much smaller scale, in cells, in what has been named collective cell migration [2–4]. During collective cell migration hundreds of cells move together, coordinately and cooperatively, in a manner not dissimilar to the murmuration of starlings. This collective cell migration has been shown to be essential for many fundamental processes, such as morphogenesis during embryo development and wound healing, and also plays a critical role in cancer invasion during metastasis [2–5].

Ecologists have been studying the collective movement of animals for much longer than cell biologists have studied the collective migration of cells, and therefore we know comparatively less about the principles that govern this latter process. Astonishingly, one of the concepts that is emerging from these studies is that the fundamental rules that control the collective migration of animals and cells seem to be very similar. Both theory and empirical observations in animals have shown that the general mechanisms responsible for the emergent group-migratory properties can be captured by simple interaction rules, such as attraction, repulsion and local alignment [6,7]. Computational models have been able to simulate collective cell migration in a variety of morphogenetic processes. In all of these models, cell repulsion is needed, similar to the repulsion shown during collective migration of animals [8]. However, the idea of cell repulsion in collective cell migration has been scarcely explored in experimental studies, probably because cell repulsion runs contrary to the concept
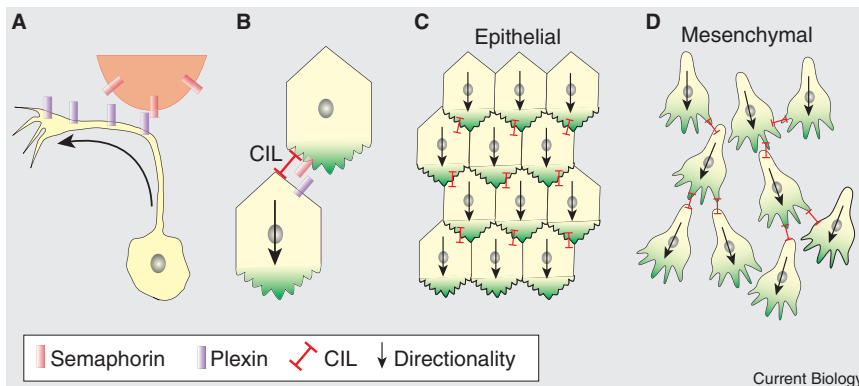
Figure 1. Contact inhibition of locomotion-mediated cell repulsion leads to collective cell migration.
(A) Interactions between Semaphorin ligand and Plexin receptor induce collapse of neuronal protrusions and a change in the direction of axonal growth. (B) In follicular cells in *Drosophila*, Semaphorin-5C interacts with Plexin A, leading to the collapse of protrusions (green shading represents protrusions). As Semaphorin-5C is localized at the anterior edge of the follicular cell and Plexin B at the posterior edge, only the posterior protrusions of each cell are collapsed. This contact-dependent inhibition of protrusions corresponds to contact inhibition of locomotion (CIL). (C) CIL spreads throughout the whole epithelium of follicular cells in *Drosophila*, generating coordinated collective cell migration. (D) A similar role for CIL in collective cell migration has been observed in mesenchymal neural crest cells.

of cells moving together during collective cell migration. Consequently, there are only a few examples of cell–cell repulsion during collective cell migration [9].

Studies of collective cell migration have been performed *in vitro* using different variants of the wound healing assay [4], or *in vivo* employing a variety of different embryos [5]. One of these *in vivo* systems is the *Drosophila* egg chamber, which has an inner germ cell cluster surrounded by follicular epithelial cells. During oogenesis, the follicle cells undergo collective cell migration, which causes the egg chamber to rotate, helping to elongate the egg [10]. In this issue of *Current Biology*, Stedden *et al.* [11] use the *Drosophila* egg chamber to characterize the role of Semaphorins in the collective migration of follicular cells. They find that Semaphorin-5C and Plexin A, a ligand–receptor pair that normally controls cell repulsion [12] (Figure 1A), are essential for the directional collective migration of follicular cells by controlling cell polarity in a contact-dependent manner (Figure 1B,C). Thus, similar to the repulsion required for the collective migration of animals [6,7], this work demonstrates that collective migration requires repulsion between follicular cells.

Stedden *et al.* [11] demonstrated that inhibition of Semaphorin-5C or Plexin A affects the migration of follicular cells and the alignment of stress fibers in the

Drosophila egg chamber. The alignment of the stress fibers has been associated with follicular cell migration [13]; it was therefore surprising to find that alignment was recovered at later stages of oogenesis. If cell migration is completely blocked, how do stress fibers become aligned later? A potential explanation is that cell migration is not completely blocked but only delayed. As follicle cell migration lasts around two days, it is not feasible to perform live imaging of this process to determine whether cell migration is delayed or blocked. The authors used an ingenious method to indirectly visualize follicle cell migration in Semaphorin-5C-depleted embryos. They forced the expression of a fluorescently tagged form of collagen in clones of follicular cells; these cells will deposit the fluorescent collagen into the basal membrane, and if the clones move they will generate fluorescent trails (comets). Using this technique, the authors found that Semaphorin-5C-depleted embryos were able to generate collagen comets, indicating that the cells are moving and therefore implying that Semaphorin-5C depletion decreases, but does not block, migration.

Importantly, Stedden *et al.* [11] found similar phenotypes following Plexin A depletion, arguing that Plexin A is the receptor for Semaphorin-5C in follicle cells. Furthermore, they demonstrated that Semaphorin-5C is localized at the

leading edge of each cell, whereas most of the Plexin A is found at the trailing edge of the cell. This complementary localization makes this ligand–receptor pair ideally suited to allow interaction between the leading and trailing edges of adjacent cells. Indeed, *in vitro* binding assays show that these two proteins interact. But how does this interaction between leading and trailing edges of adjacent cells, mediated by Semaphorin–Plexin interactions, result in collective directional migration?

Semaphorin and Plexin are well-characterized molecules involved in cell repulsion. Early studies in neurons demonstrated that Semaphorins cause dramatic changes to cell morphology, including the rapid collapse of cell protrusions [14] (Figure 1A). These changes occur in many other cell types and are mediated by Plexin, which negatively regulates the stability of the actin and microtubule cytoskeleton and reduces cell adhesion [14,15]. Consistently, Stedden *et al.* [11] proved that depletion of Semaphorin-5C or Plexin interferes with the protrusions of follicular cells. During collective cell migration, protrusions of all follicle cells point in the direction of migration, providing the correct cell polarity for their directional movement [10]. Inhibition of Semaphorin-5C leads to protrusions being formed in random orientations [11], thereby affecting collective cell migration. In addition, the authors provide evidence that Semaphorin-5C also interacts with Lar, a receptor protein tyrosine phosphatase involved in follicle cell migration [16].

The model that emerges from these results is that a follicle cell expressing Semaphorin-5C in its anterior edge will signal via the Plexin A receptor present in the trailing edge of the anteriorly located cell, inducing a collapse of the protrusion at the posterior end of the anterior cell, leaving this cell with only an anterior protrusion (Figure 1B). This leads to planar polarization of cells within the epithelium, with each protrusion pointing anteriorly in the direction of migration (Figure 1C).

This mechanism of contact-dependent cell polarity corresponds to the process called contact inhibition of locomotion (CIL), which is involved in the collective migration of amphibian and zebrafish neural crest cells [9] (Figure 1D). Although neural crest cells and follicle cells both migrate collectively, they differ in that

neural crest cells are mesenchymal whereas follicle cells are epithelial. It has been suggested that collective migration of mesenchymal and epithelial cells could use different mechanisms [17], but the work by Stedden et al. [11] indicates that these two cell types share CIL as the driving force to polarize the collective. This work also sheds light on the principles behind CIL, as it shows that this process can be present in a group of cells that exhibit protrusions pointing in the same direction of migration, as has been described for chick neural crest [18]. It will be interesting to know whether other collectively migrating cells use CIL as one of the mechanisms to coordinate their migration, even if the molecular mechanism of this CIL differs in other systems [19].

While this work demonstrates a definitive role for Semaphorins and Plexins in collective cell migration, it also raises some questions. The model works nicely to transmit planar cell polarity from a cell that is already polarized, but how is the polarization established in the first place? Is the Semaphorin–Plexin interaction a mechanism to initiate polarity or to amplify a previously existing polarity? Despite these questions, we can confidently say that, similar to the repulsion between locusts that is based on cannibalistic behaviour and is essential for collective migration [20], cell repulsion is indispensable for the collective migration of cells.

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Sleep: Never Wasted but Often Too Short

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Sleep duration and food intake are interconnected and important for health. New research shows that reducing sleep across five nights leads to more snacking after dinner and metabolic disturbances, which *ad libitum* weekend sleep could only partially compensate for.

The weekend: the end-of-the-week island of liberty and freedom. Weekends provide room to recover from the workweek, offering time for extended leisure activities with friends and family, and — perhaps most treasured of all — more time to sleep. It is not an understatement that weekends, for many people, are a sleep refuge. Epidemiological research shows that about 35% of American adults on average sleep less than seven hours per night [1] and about another third sleep fewer than six hours per night. Specific demographic groups sleep even less, for instance, active military personnel who