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Cell traction in collective cell migration and morphogenesis: The chase and run mechanism

Andrés Szabó and Roberto Mayor*
Department of Cell and Developmental Biology; University College London; London UK

Directional collective cell migration plays an important role in development, physiology, and disease. An increasing number of studies revealed key aspects of how cells coordinate their movement through distances surpassing several cell diameters. While physical modeling and measurements of forces during collective cell movements helped to reveal key mechanisms, most of these studies focus on tightly connected epithelial cultures. Less is known about collective migration of mesenchymal cells. A typical example of such behavior is the migration of the neural crest cells, which migrate large distances as a group. A recent study revealed that this persistent migration is aided by the interaction between the neural crest and the neighboring placode cells, whereby neural crest chase the placodes via chemotaxis, but upon contact both populations undergo contact inhibition of locomotion and a rapid reorganization of cellular traction. The resulting asymmetric traction field of the placodes forces them to run away from the chasers. We argue that this chase and run interaction may not be specific only to the neural crest system, but could serve as the underlying mechanism for several morphogenetic processes involving collective cell migration.

Comment

Collective cell migration, the orchestrated movement of large cell masses, plays an important role in a wide variety of developmental, physiological and pathological processes. Important aspects of the phenomenon include cell-cell adhesion, cell-matrix adhesion and force generation, which have been examined using methods of mechanics and statistical physics to identify key mechanisms acting behind collective migration, such as the interplay of crowding and volume exclusion, or plithotaxis, the cells’ tendency to reduce inter-cellular mechanical shear stress. These studies demonstrate the importance of mechanical forces in shaping the cell collective, complementing the guidance of various biochemical signals. Much of the attention has been given to the migration of tightly connected epithelial cells where group coherence is supported by the architecture of the tissue and thus cells are forced to remain in close vicinity throughout motion. Similarly important but less studied is the collective migration of mesenchymal cells, where coherence has to be maintained by less apparent cellular interactions.

The Migrating Neural Crest

A prominent example of mesenchymal collective migration during development is the migration of the neural crest (NC). During early embryogenesis, these cells travel large distances throughout the body in a loosely associated cluster to give rise to nerves, bones, connective tissue and muscle. In accordance with its ubiquitous nature, NC migration is robust and highly conserved among vertebrates.

NC cells are specified at the edge of the neural plate during neurulation. They separate from their surrounding tissues by undergoing an epithelial-to-mesenchymal transition, after which the mesenchymal NC invades the neighboring tissues. In the head, the cranial NC invades the adjacent epithelial placode cells in streams.
leading to pattern formation by segregating into separate branches. What drives this segregation, or what evolutionary advantage does this segregation carry is still not clear. Several inhibitory clues have been reported at the edge of the NC streams that restrict the lateral migration of the group, which could suggest a pre-patternning mechanism. The size of the migratory collective depends on its position along the body axis: while in the head the cranial NC (CNC) forms larger collectively moving groups, in the trunk the streams can be as thin as a single cell and perform chain migration.\textsuperscript{13} The migration streams can be as thin as a single cell and actively moving groups, in the trunk the CNC forms larger collections,\textsuperscript{14} although the effect of placodes on NC development was not explored in detail. During migration placode cells border the invading streams and avoid mixing. NC expresses N-cadherin and placodes N- and E-cadherins, allowing them to form N-Cadherin adhesions between placodes (PLs) and NC.

A recent report by Théveneau et al.\textsuperscript{20} revealed the interaction between NC and PLs that serves as a source of directed and prolonged collective migration of these 2 adjacent cell populations. The mechanism is based on 2 opposing effects: while PLs attract the NC by secreting the chemotactic Sdf1, PLs exhibit CIL-like behavior upon contact with the NC causing them to run away from the chasing NC.

The “Chase and Run” Mechanism in the Neural Crest - Placode System

Focused on unveiling the chase and run interaction between NC and PLs, Théveneau and colleagues explored the mechanism in detail. During NC migration in Xenopus laevis and zebrafish embryos, PLs were observed to flee from the invading NC cells which migrated into the former place of the PLs. When a NC and a PL explant are cultured in vicinity, the NC cluster undergoes chemotaxis toward the PL cluster in an Sdf1-Cxcr4 dependent manner (Fig. 1A “chase”). Although the PL explant is largely immobile when cultured in isolation, traction force microscopy revealed that PL cells exert significant traction at the edge of the cluster (Fig. 1A, blue arrows). Pulling the substrate toward the center of the cluster generates an isotropic traction field under the PL explant. Upon contact with the NC, the NC and PL cells form a transient but fully functional N-Cadherin based adhesion complex (Fig. 1A, red bar). Following the establishment of cell-cell adhesion, focal adhesions (FA) are downregulated at the point of contact (Fig. 1A, blue bars) and, concomitantly, protrusions in the NC are destabilized by the N-Cadherin engagement, possibly due to the reduction of FAs, causing the NC to stall, repolarize and separate from the PL explant (Fig. 1A “run”). On the other side of the contact, the loss of FAs significantly perturbs the PL traction, resulting in an asymmetric traction profile of the PL cluster that expels the PLs away from the NC. After the contact is broken by the NC CIL and the PL propulsion (“run”), FAs are re-formed allowing the NC to pursue the chase.

While the exact molecular mechanism of how N-Cadherin engagement results in destabilization of protrusions remains to be investigated, the finding of Théveneau et al.\textsuperscript{20} already provide a novel mechanism for generating a highly efficient directional migration. Once in near vicinity, this mechanism provides a means of preventing mixing and promotes the formation of clear boundaries between populations destined for different fates. It is the interaction of the 2, otherwise less motile or less persistent, populations that gives rise to a highly ordered motion through an asymmetric ratchet mechanism based on traction forces.

“Chase and Run” as a General Mechanism for Directional Migration

The chase and run behavior is based on 2 generic mechanisms: paracrine chemotaxis and CIL. Chemotaxis has been known to be present in a wide range of cellular systems. CIL is somewhat less studied, but it is still present in various cell types such as fibroblasts, retina, leukocytes, or nerve fibers.\textsuperscript{21} Therefore, we argue that this mechanism is not specific to the NC and PL system, but it is likely to be a more general mechanism for directional migration.

The requirement for interaction between distinct, neighboring populations is not uncommon. During kidney morphogenesis, ureteric bud outgrowth is driven by paracrine chemotaxis toward GDNF secreted by the neighboring metanephric mesenchyme.\textsuperscript{22} Whether the mesenchyme is pushed passively, or it exhibits CIL and actively retracts from the invading epithelial bud using a chase-and-run mechanism (Fig. 1B), remains to be explored. Another example of highly persistent collective migration during development is the migration of the posterior lateral line primordium (PLLp) in
zebrafish. In the primordium, cells at the leading edge of the cluster secrete FGF as a result of active Wnt signaling and the same signal renders the leader cells immune to FGF chemotaxis by inhibiting FGF receptor signaling. The secreted FGF, however, triggers chemotaxis in the follower cells. A recent study showed that close vicinity of leaders and followers is essential in PLLp migration. When the leader and follower populations were separated using laser ablation, the directed migration of the leaders stopped. It is tempting to speculate that the FGF-induced “chase” is accompanied by a “run” mechanism similar to the NC-PL system (Fig. 1C), and by distancing the 2 populations by ablation the essential interaction is prohibited.

A typical pathological example where a demarcation of 2 distinct populations is present is the solid tumor – stroma interface. Fibroblasts secrete various diffusing signals, including fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and Sdf1, that prompt cancerous cells to proliferate and invade the stroma. Tumor associated fibroblasts are known to be involved in metastasis by leading cancerous cells out of the tumor. Hence, tumor cells are able to acquire the ability to chase fibroblasts and, possibly also the ability to cause “run” behavior in fibroblasts (Fig. 1D), providing them with a high metastatic probability that could lead to a significant selection advantage. However, it is essential for the chase and run mechanism that tumor cells and fibroblasts exhibit CIL upon contact with one another. This may depend on the specific cell types, as exemplified in early experiments showing behaviors ranging from the complete absence of CIL between tumorous and normal cells to full CIL (for review see Heaysman).

In conclusion, the chase and run behavior represents a general ratchet mechanism that could play an important role in several morphogenetic and pathological processes involving collective cell migration. The mechanism gives rise to an enhanced directional migration emerging from the interaction of 2 distinct populations. An excitable population (the PL in the NC-PL system) serves as a long-range activator of the chasing population (NC) in the form of chemotaxis and polarizes the system by prompting the followers to move in a distinct direction, while upon contact the movement is halted by a short-range (contact-dependent) inhibition. During this process, the attractant source is displaced, and such dynamic “source and sink” cellular systems are able to generate robust directional migration.

Figure 1. Chase and run as a general mechanism emerging from the interaction of 2 cell populations. Neural crest (NC) cells are attracted to placodes (PLs) via Sdf1 chemotaxis (A, chase). The PL cluster applies strong traction on the substrate symmetrically at the edge of the cluster (blue arrows) via focal adhesions (FA, blue bars). Upon contact the NC and PL form fully functional cell-cell adhesions via N-Cadherin (red bars) which halts the forward motion of NCs via contact inhibition of locomotion (CIL) and downregulates FA at the cell-cell contact (A, run). The resulting asymmetric traction of the PLs (blue arrows) expels them from the contact, prompting them to run from the NC. Once the contact is broken, the chase phase resumes. This general mechanism might play a role in other morphogenetic processes, such as kidney development (B), where the mesonephric mesenchyme is attracting cells of the ureteric bud; posterior lateral line primordium (PLLp) migration (C), where the front of the PLLp is attracting the follower group via FGF chemotaxis; or fibroblast led tumor metastasis (D), where the fibroblasts could aid the tumor cells to enhance their directionality through the chase and run mechanism.
and run” is explained based on purely mechanical traction forces, underlining the importance of the physics of cell migration.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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