



Neighborly relations during collective migration

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The collective migration of sheets, cohorts, chains or streams of cells contributes to embryogenesis, tissue remodeling and repair as well as to cancer invasion. The functional coordination between neighboring cells is at the heart of collective migration, during which cells migrate with a similar speed in an identical direction. Far from being the result of the simultaneous migration of isolated cells, collective migration relies on the intercellular communication between migrating cells. Although the mechanisms of cell coordination are far from being completely understood, accumulated evidence show that exchange of mechanical and chemical information by direct intercellular contacts and by soluble extracellular signals orchestrate the coordinated behavior of collectively migrating cells.

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Introduction

During development, tissue repair or tumor spreading, cells frequently migrate in a collective manner, forming sheets, clusters, chains or other multicellular arrangements. By contrast to the migration of single cells such as leukocytes chemotaxing in the direction of an inflammatory site, collective migration corresponds to the active coordinated movement of physically connected cells and can be distinguished from convergence-extension which essentially involves cell rearrangements, without active migration. Gastrulation, *Drosophila* dorsal closure as well as wound healing are classical examples of cell sheets migrating collectively. Border cells in the *Drosophila* ovary, lateral line primordium cells in zebrafish exhibit a collective movement of cells. Migration of chains of endothelial cells is a classical feature of angiogenesis both during development, tissue regeneration or tumor vascularization. Finally,

tumor invasion frequently relies on the collective migration of cell sheets, chains or groups. In these examples, cells continuously interact with one another maintaining strong and yet plastic connections. However, collective migration can also be observed when cells, like trunk neural crest cells, migrate in chains or streams with loose intercellular contacts. Collective migration is characterized by the functional coordination between neighboring cells. Each cell of the group migrates in a similar direction and at a similarly speed, so that the integrity of the cell group remains intact during movement. Whether cells are tightly connected or only meet occasionally, the constant communications between individuals, like in a friendly neighborhood, is essential to orchestrate coordination within the group. In particular, collective migration requires a subtle balance between contact inhibition of locomotion and the maintenance of cell interactions [1]. The adhesive contacts between migrating cells are counterbalanced by the repulsion that results from contact inhibition of locomotion. Together these interactions promote the migration of leader cells and orchestrate the polarization and migration of the following group of cells. Like in single cell migration, the small G proteins of the Rho family play a key role in regulating cytoskeletal rearrangements which promote cell migration. Rac and Cdc42 promote actin polymerization and play a key role in the generation of protrusive leading processes, whereas Rho controls cell contractility [2]. Here, I will review the recent findings showing that migrating cells can send, receive and share information transmitted by intercellular contacts, mechanical forces and soluble factors to achieve a coordinated migratory behavior.

Shaking hands: exchanging information by direct contacts

Communication through intercellular contacts is mainly mediated by AJs (AJs) and the Wnt/PCP (Planar Cell Polarity) pathway, which both signal to Rho GTPases to regulate the cytoskeleton. AJs have been observed at cell–cell contacts during collective migration and classical cadherins are essential for the collective migration of a wide number of cell types [3,4]. Changes in cadherin isoforms are crucial in epithelial mesenchymal transition both during development and in cancer progression [4]. By contrast, the complete loss of AJs induces the dissociation of cell groups and the random migration of isolated cells [5,6]. AJs between collectively migrating cells are important but AJs between the migrating cells and the non-migrating cells of their microenvironment can also promote collective migration [7**]. If not the nature, the expression level of cadherin distinguishes the migrating cells from their environment. In the *drosophila*,

E-cadherin expression must be higher in border cells than in the neighboring nurse cells to sustain directed collective migration [7**]. The essential role of AJs in the control of collective migration calls for a tight regulation of cadherin levels at the plasma membrane. A recent study investigating the life time of surface cadherin during the migration of the zebrafish lateral line primordium show that AJs are less stable at the front than at the rear of the cell group [8*]. From a uniform distribution in leader cell membrane, N-cadherin (Cdh2) starts to form apical clusters in the transition zone between the leader cells and their followers, suggesting that leader cells acquire a mesenchyme-like organization. Although the authors show that E-cadherin (Cdh1) is also expressed in these cells, how its expression pattern and its localization vary across the front-rear axis of the cell group remains to be determined. Integrin-mediated signaling has been shown to modulate cadherin expression during the migration of embryonic *Drosophila* salivary gland [9]. α PS1 β PS integrins induce, via Rac1, a downregulation of E-cadherin expression in the distal gland cells, which is required for the migration of both distal and proximal gland cells [9]. During 2D and 3D *in vitro* collective migration, in the leading cells, which have a contact free cell front, AJs undergo a continuous retrograde treadmill. The retrograde flow of AJs is sustained by the polarized recycling of cadherins from the rear to the front of the cells, where cadherin complexes accumulate before forming new AJs with their direct neighbors or with other cells allowing a switch in cell position [10**].

The distribution of direct intercellular contacts clearly distinguishes the leader cells, located at the front of the group. The anisotropic distribution of AJs in leader cells gives spatial cues and promotes cell polarization towards the free cell edge [11] and the collective directed migration of cell sheets [6,12]. The role of AJs relies on their interplay with integrin-mediated interactions between the cell and the extracellular matrix. *In vitro* models using adhesive micropatterns to control the localization of cell–cell and cell–substrate interactions, have shown that AJs locally inhibit interactions between the cell and the substrate [13,14], which results in the polarized localization of integrin signals leading to localized cell protrusion sheets [6]. The N-cadherin-p120 catenin complex restrict integrin α 5 to contact free regions [15**]. The anisotropic distribution of cellular interactions also promotes the polarized rearrangement of the cytoskeleton [13,16]. AJs control the orientation of the nucleus-centrosome axis and the polarization of the microtubule network [6] which facilitates cell migration [17]. The polarity protein Par3 is associated with AJs and interacts with the microtubule associated motor dynein during wound-induced polarization of fibroblasts [18]. Par3 also controls microtubule catastrophe at contact sites between neural crest cells where N-cadherin and cadherin 11 are

present [19]. In this case, Par3 was shown to bind and inhibit the Rac-GEF Trio, leading to the localized inhibition of Rac. Reciprocally, microtubules play a key role in the stabilization of AJs in the follower cells of the lateral line primordium [8*]. In this model, the changes in cadherin localization correlates with changes in the orientation of the centrosome-nucleus axis [8*].

Wnt/PCP (Planar Cell Polarity) signaling, which plays a key role in various developmental processes including collective cell movements during convergence-extension, also contributes to the global polarization of cell groups or sheets actively migrating in a collective manner (reviewed in [20,21]). At intercellular contact sites, the transmembrane molecules Frizzles (Fz) and Strabismus (Stbm) expressed on the adjacent cells interact. The contribution of PCP signaling relies on the polarized distribution of its components, which leads to a polarized distribution of downstream signals, involving Rho GTPases and cytoskeleton regulation [20]. Furthermore, PCP signaling may indirectly affect collective migration by controlling AJs. The transmembrane protein Vangl2 recruits Rac1 at the plasma membrane [22], which impairs AJs and normal neural tube development [23]. Like AJs, PCP can also influence cell interaction with the extracellular matrix [24] and indirectly trigger directed migration. Moreover, PCP signaling participates in the localized activation of actin polymerization and polarized organization of intracellular structures in migrating epithelial sheets [25]. The PCP protein Fritz has also been shown to control the localization of septins which could contribute to the asymmetric organization of the cytoskeleton [26].

Both AJs and PCP signals regulate Rac and Rho to control contact inhibition at cell–cell contacts and protrusion of the contact free edge (reviewed in [27]). AJs and PCP signaling at cell–cell contacts restrict phosphoinositide 3-kinase and Rac activities, and consequently cell protrusion, to contact free regions [12,15**]. In border cells, Rab11 serves as a sensor of Rac activity in adjacent cells and contributes, via cell–cell communication, to restrict Rac activity to the leading cell [28]. The N-cadherin- β catenin complex promotes the recruitment of myosin II light chain and polymerized actin at cell–cell contacts [15**]. Newly formed AJs during collective migration of epithelial cells, also induce the recruitment of Myosin IXA [29]. The depletion of Myosin-IXA alters the mechanotransduction at AJs and prevents collective cell migration. Rho activity and acto-myosin contractility can either stabilize AJs or, when stronger, induce cell contraction and repulsion. During neural crest cell migration, high Rho activity at cell–cell contacts promotes cell repulsion and contact inhibition and keep cells loosely connected [3,30]. By contrast, in a cohesive migrating cell group, Rho and acto-myosin activity must be downregulated at intercellular contacts to prevent cell dissociation.

DDR1 (Depletion of Discoidin Domain Receptor 1) is a single transmembrane protein which associates with E-cadherin, and binds to Par3. In invading groups of cancer cells, DDR1-mediated recruitment of Par3 to AJs promotes the localization of RhoE, which, together with p120RhoGAP, antagonizes Rho and limits acto-myosin contractility [31]. Analyses of the coordinated cellular movements resulting in cell intercalation reveal that PCP signals can locally activate Rho and ROCK leading to the phosphorylation of Par3 and preventing Par3 association with aPKC and its cortical localization at specific cell borders [32,33]. The subtle balance between Par3 and Rho activity at cell–cell contacts controls the strength of intercellular interactions within the cell group. At the lateral and rear edges of the cell groups, the absence of AJs leaves acto-myosin contractility high [34].

Recently, the Hippo pathway has been shown to also contribute to collective migration in *Drosophila* border cells [35**]. The Hippo pathway is involved in contact-inhibition of cell proliferation in epithelial tissues of *Drosophila* and mammals (reviewed in [36,37]). The localization of upstream components of the Hippo pathway, including Kibra, Expanded and Merlin is restricted to intercellular contacts inside border cell clusters. In absence of Hippo signaling, the functional organization of actin at the outer rim of the border cells is altered and cells cannot move directionally [35**]. In this case, Hippo signaling acts through the direct regulation of actin dynamics by phosphorylation of Ena and independently of transcription regulation. In this context, The Hippo pathway contributes to the discrimination between cell edges located inside the migrating cell group and those situated at the external border of the group. Whether this distinction is also important to maintain the cohesion of larger migrating cell cohorts or cell sheet remains to be investigated.

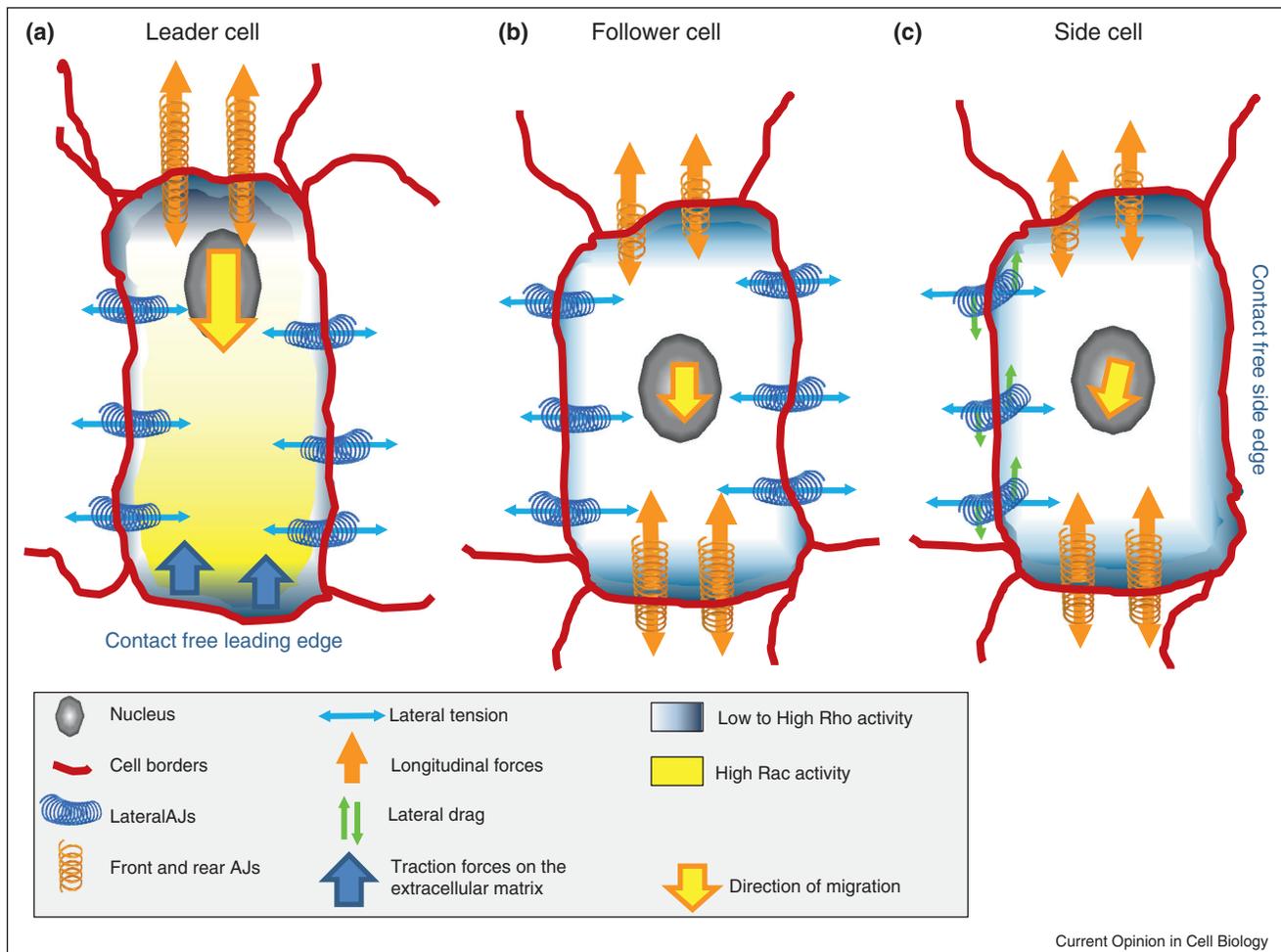
Push-me, pull-you: physical pressures from the neighbors

Viscoelastic interactions between neighboring cells present a simple explanation for the initiation of cell migration pushing, for instance, the wound edge cells to migrate outward [38,39]. Using micropatterning to confine cells to limited spaces, B. Ladoux and colleagues have shown that the geometrical constraints of the environment influence collective migration by impacting on cell density. At higher densities, cell migration is faster, more directed and more persistent [40,41]. In addition, AJs play a key role in sensing and transmitting mechanical tension between contacting cells. External forces induce changes in the conformation and composition of AJs leading to a better coupling to the actin cytoskeleton (reviewed in [42]). Moreover, tension exerted on cell–cell contacts also promotes the recruitment of plakoglobin and keratin filaments to AJs [43].

The balance of forces generated by integrin-mediated adhesion to the extracellular matrix and AJs is crucial in the control of leader cell migration (Figure 1a). Mapping forces across a moving epithelial cell sheet shows that leader cells generate most of the pulling forces towards the substrate [44**]. The crosstalk between integrin and cadherin mediated adhesion allows migrating cells to adjust the intercellular tension depending on the substrate stiffness [45]. Leading cells can sense substrate stiffness and relay this information to the followers over large distances through myosin-dependent mechanical stress. Collective migration is faster, more directed and more persistent on stiffer substrates [45]. Conversely, the adhesion forces exerted between neighboring cells through AJs influence the tension forces applied to the extracellular matrix [39]. Using a combination of biophysical and imaging methods, M. Reffay and colleagues have shown that RhoA activity is higher at the leading edge where it generates pulling forces, which are transmitted to several rows of follower cells through AJs (Figure 1). Recent work in the *Drosophila* tracheal model shows that constitutive activation of Rho in migrating clusters impairs the migration of the leader cells, which are incapable of migrating unless catenin is downregulated to weaken AJs [46*]. In this model, inhibition of Rho strongly perturbs the AJs leading to cell detachment from the cell cluster [46*]. However, in migrating epithelial monolayers, RhoA inhibition in the leader cells does not prevent collective migration but induces a switch in the nature of the main forces involved in cell movement. In this case, pushing forces generated by the cells within the monolayer can promote the migration of the whole monolayer [44**]. When this force is abrogated, the pushing-mode of collective migration is likely to result from the release of physical constraints at the wound edge and from the visco-elastic properties of the cells. This mechanism may only apply to cells that can reach high densities like cancer cells and may not operate during the migration of cell clusters.

Pulling forces generated by leader cells are then transmitted via longitudinal acto-myosin cables to followers (Figure 1B), so that the leading cells actively pull forward several rows of followers [44**]. *In vitro* and *in vivo* photoablation studies have shown that the leader cells are required for successful migration of the followers [47,48]. In follower cells, the intensity of forces exerted through cell–cell contacts between adjacent cells is responsible of cell coordination [7**,49]. A FRET-based traction sensor was used in *Drosophila* border cells to show that the tension exerted on cadherin decreases from the front to the rear of the cluster [7**]. AJs can transmit traction forces across large epithelial sheets [50]. Down-regulation of N-cadherin in a monolayer of migrating astrocytes leads to the detachment of the leading cells from the rest of the monolayer and to an increase in the migration speed of these cells [6]. Cells tend to elongate

Figure 1



Forces exerted between adjacent cells within a collectively migrating group. The distribution of cell-cell contacts and the balance of forces distinguish the leader cells (a), the followers (b) and the cells located at the edge of the cell group (c). Leader cells generate traction forces (filled block arrows) via integrin-mediated adhesion to the extracellular matrix. These traction forces are transmitted through AJs (yellow springs) to the followers which resist these pulling forces (orange double arrows). While most forces are aligned with the direction of migration, lateral forces are also transmitted by AJs (blue springs) and participate to the mechanical coupling of adjacent cells. Finally, lateral AJs support a lateral drag steering (green arrows), which may contribute to the local coordination of cell movement and is likely to be important at the lateral edges of the cell group. Acto-myosin contractility is responsible for the generation of forces throughout the cell and is primarily controlled by the activity of the small GTPase Rho (which activity is shown in blue). By contrast, Rac activity (in yellow), which has been shown to be higher in leader cells, promotes membrane extension and cell protrusion.

and migrate in the direction of the principal stress [49] and the viscoelastic interactions between adjacent cells contribute to long-range collective migration of cell sheet [51]. At the edge of the cell group, AJs may contribute to the coordinated polarization and faster migration of the cells through a lateral-drag steering mechanism [52] (Figure 1C). Lateral mechanical coupling through AJs may also play a key role during cell sheet migration, AJs serve as a link between the transverse actin cables of the adjacent leader cells [10]. Mechanical coupling between adjacent cells may be important when a migrating cell sheet encounters a non-adhesive region [53]. The leader cells, which cannot migrate on the non-adhesive substrate,

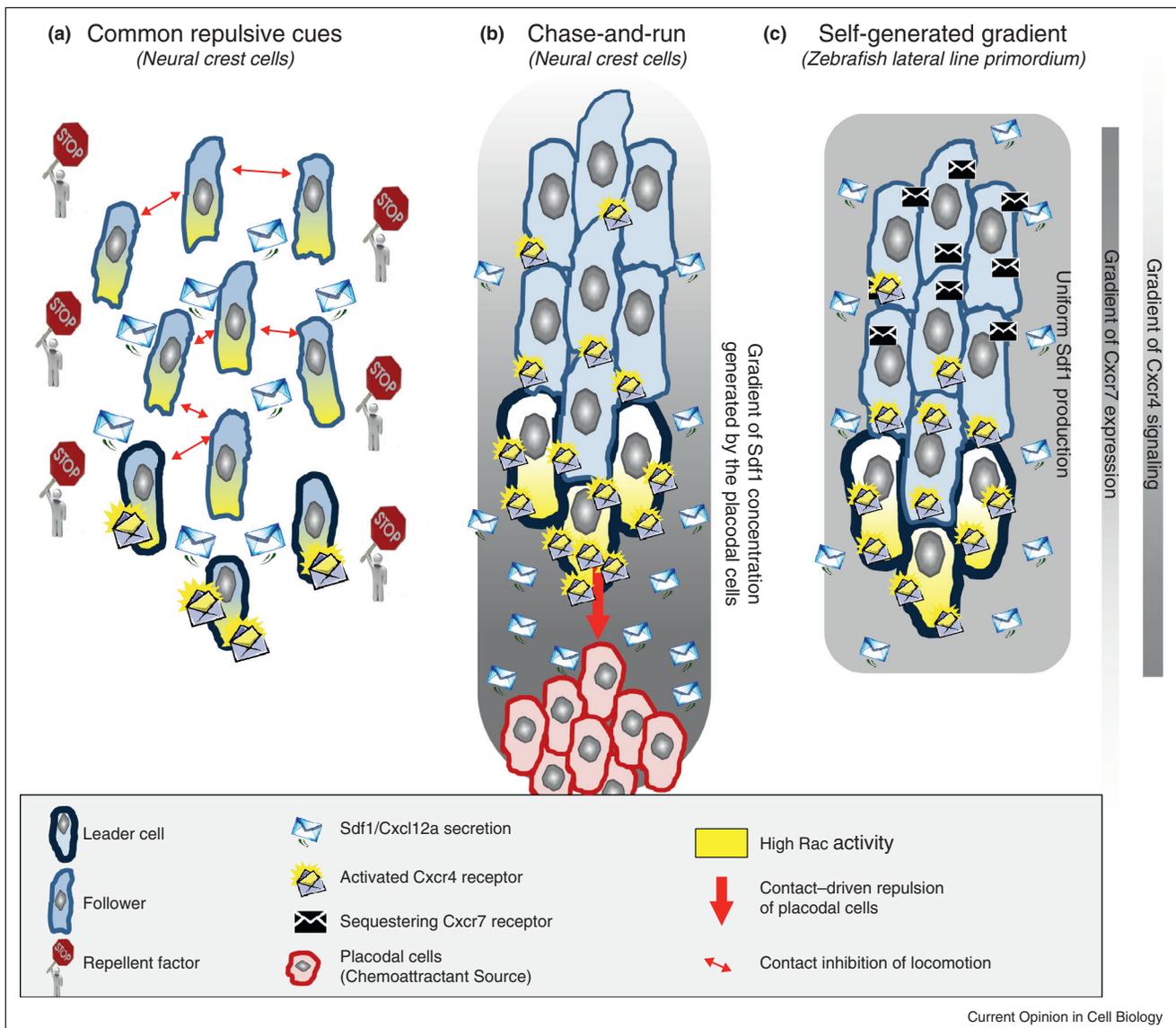
change morphology and tend to move around the free space. Nevertheless the traction forces remain constantly oriented towards the front [53]. In the case of *Drosophila* dorsal closure or wound healing of a small lesion, lateral coupling allows the formation of a strong actin cable across the front of the cell sheet that directly contributes to the forward movement of the cell monolayer [54]. In a situation where the front edge cannot close on itself, such as in a large scratch wound assay or during collective invasion, this coupling might contribute to the coordination of actin dynamics. In addition, since the actin retrograde flow promotes nucleus positioning, it may improve the collective polarization of the leading cells.

Sending messages: sharing information via diffusive factors

Collectively migrating cells can produce paracrine factors that will contribute to their coordination (Figure 2a). This was initially demonstrated in *Dictyostelium discoideum*, where the binding of cAMP, which serves as a chemoattractant, leads to the production and secretion of additional cAMP. This signal relay increases the number of cells that receive the signal, the distance between responsive cells

and the initial source of chemoattractant and more importantly increases the speed and directionality of migration of individual cells [55]. A similar mechanism has recently been documented in neural crest cells which produce complement factor 3a (C3a) and express its receptor C3aR [56]. C3a paracrine attractive signals activate Rac and promote cell regroupment while preventing dispersion. Similar paracrine signals may also be involved in coordinating tumor cell invasion. In squamous cell

Figure 2



Exchange and sharing of soluble information within a migrating cell group. Migrating cells respond to soluble repellent molecules (stop signs) and attractant molecules (envelops). **(a)** In loosely connected cell groups such as in stream of neural crest cell, cell-cell contact locally inhibits Rac and induces Rho-mediated contact inhibition of locomotion. Repellent factors prevent the escape of migrating cells. **(b)** and **(c)** In cohesive groups, cell-cell contacts associated with a moderate Rho activity maintain the group integrity. Chemoattractant gradient are reinforced or even created by the migrating cell group. **(a)** Leader cells can relay the signal via paracrine secretion. **(b)** Followers can sequester chemoattractant molecules and serve as a sink. The gradient of receptor activity can be reinforced by the higher expression of the receptor in leader cells and the accumulation of the receptor at their leading edge. **(c)** The source of chemoattractant (here placodal cells) can move synchronously with the migrating group. Cells migrating towards the source of chemoattractant, eventually collide with the secreting cells and, by contact inhibition, induce their migration forward.

carcinoma, Snail induces the expression a Cyr61 (Cystein rich 61, CCN1), a secreted protein which stimulates the collective migration of the tumor cells [57]. Paracrine signals can be amplified by the specification of leaders and followers within the migrating group, as in the zebra-fish lateral line primordium where FGF is produced by the leading cells and specifically signals in the trailing cells [58] (Figure 2a).

Attractive or repulsive factors can act simultaneously on migrating cells to direct their migration in a common direction (Figure 2a). Repellent signals from ephrins and class 3 semaphorins prevent the escape of isolated neural crest cells [27]. Positive chemotactic responses shared by collectively migrating cells guide them towards their target sites. Sdf1 (Stromal Cell derived factor-1) act as a powerful chemoattractant during neural crest migration [59,60]. Interestingly, the placodal cells which produce the chemoattractant move as the neural crest cells migrate so that the chemoattractant source remains at a relatively close distance facilitating chemotaxis during the entire migratory process [61**] (Figure 2B). Alternatively, a cell cohort can self-generate an Sdf1 gradient as recently shown independently by two groups studying the zebra-fish lateral line primordium [62**,63**]. All cells of the primordium express Cxcr4b, a Sdf1-receptor mediating chemotactic response through Gβ1 signaling [64]. However Sdf1 is generated as a uniform stripe. Using different reporters to investigate Cxcr4 activity across the primordium, both groups elegantly provide evidence for a gradient of receptor activity suggesting that the gradient of Sdf1 is self-generated [62**,63**] (Figure 2b). They further show that another Sdf1 receptor, Cxcr7 is preferentially expressed in the cells at the rear of the primordium. This forms a local sink for Sdf1, constantly sequestering 1% of the total Sdf1 and generating a steady linear gradient with a slope of 7% per cell [62**]. When the gradient of Sdf1 signaling decreases below 3% per cell, the speed and direction of migration of the primordium are severely perturbed.

Collectively migrating cells react to chemoattractant gradients and chemotax more efficiently together than as isolated cells [12]. Differences in cellular responses to chemoattractant can result from the position of the cells within the migrating group. In wound-induced directed collective migration of epithelial sheets, the cell response to TGFβ is modulated by the cell density. At the wound edge where the cell density is lower, the TGFβ-induced Erk activation is stronger, leading to a faster migration of wound edge cells [65]. In *Drosophila* border cells, the growth factor receptors PVR and EGFR, signaling through Rac, stabilize the protrusion of leader cells towards the front [66]. The polarization of the leader cells induces an asymmetric distribution of the exocyst complex and of recycling endosomes [67*]. This promotes the accumulation of PVR and EGFR at the front of the

leader cells and increases the chemotactic response (Figure 2). PVR/EGFR signaling to Rac is further enhanced by the increased tension exerted on cadherin-mediated junctions of the leading cell [7**]. Interestingly, genetic manipulation leading to the specific activation of receptor signaling or of Rac in one cell of the cluster is sufficient to direct the cluster movement, indicating that cells affect each other and that the chemotactic signal perceived by one cell affects the behavior of the entire group of cells [68]. The necessary and sufficient function of leader cells in directing collective migration in response to chemoattractants was further demonstrated in the *Drosophila* tracheal systems, where cells clusters migrate in response to FGF (Fibroblast Growth Factor) [46*]. Lines of evidence suggest that leader cells present specific characteristics compared to the followers.

During collective migration, cells exchange physical and chemical information by direct contacts or via soluble factors. Leader cells play a key role in interpreting the environmental cues and in controlling the collective behavior either through mechanical coupling or through their participation to the generation of chemical gradients. The specificity of leader cells can result from the differential expression of given membrane receptors and/or soluble factors. Whether leader cells also display particular intrinsic mechanical properties remains to be determined. An important question that remains is what initial signal triggers the formation of leader cells. In physiological conditions, environmental cues such as the release of chemoattractants, changes in gene expression triggered by developmental processes are essential to the specification of leader cells and to the initiation of collective migration. During tumor invasion, the interaction of migrating tumor cells with their environment is essential to support continuous invasion, but the initial signal inducing the formation and the migration of leader cells remains to be identified.

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