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Review

Cell migration during morphogenesis

Andy Aman, Tatjana Piotrowski *

University of Utah, Department Neurobiology and Anatomy, 20N Medical Drive, MREB 401, Salt Lake City, UT 84132, USA

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ABSTRACT

During development, functional structures must form with the correct three-dimensional geometry composed of the correct cell types. In many cases cell types are specified at locations distant to where they will ultimately reside for normal biological function. Although cell migration is crucial for normal development and morphogenesis of animal body plans and organ systems, abnormal cell migration during adult life underlies pathological states such as invasion and metastasis of cancer. In both contexts cells migrate either individually, as loosely associated sheets or as clusters of cells. In this review, we summarize, compare and integrate knowledge gained from several in vivo model systems that have yielded insights into the regulation of morphogenic cell migration, such as the zebrafish lateral line primordium and primordial germ cells, Drosophila border cell clusters, vertebrate neural crest migration and angiogenic sprouts in the post-natal mouse retina. Because of its broad multicontextual and multiphylletic distribution, understanding cell migration in its various manifestations in vivo is likely to provide new insights into both the function and malfunction of key embryonic and postembryonic events. In this review, we will provide a succinct phenotypic description of the many model systems utilized to study cell migration in vivo. More importantly, we will highlight, compare and integrate recent advances in our understanding of how cell migration is regulated in these varied model systems with special emphasis on individual and collective cell movements.

Introduction

Cell migration is a widespread and complex process crucial to the morphogenesis of animal body plans and individual organ systems. Cells are specified in one region of the embryo during gastrulation and then migrate extensively before they reach their target. Additionally, reactivation of cell migration processes underlies invasion and metastasis of human cancers, making the study of morphogenic cell movements clinically relevant. Whether occurring during normal development or under pathological conditions, cells can either migrate individually or in groups. Individual cell migration has been noted in few, but nonetheless essential biological processes *in vivo*. Primordial germ cells (PGCs), leukocytes and hematopoietic stem cells, for example, migrate as individual cells (Friedl et al., 2001). In contrast, the number of contexts in which collective cell migration is known to occur has been increasing steadily in recent years. In *Drosophila*, this mode of cell migration is employed during border cell migration and tracheal development (Montell, 2003). In vertebrates, besides the widely studied collective migratory events of gastrulation and neural crest cell development, a key role for collective cell migration has been noted in vascular sprout and pronephros development (De Smet et al., 2009; Teddy and Kulesa, 2004; Vasilyev et al., 2009), as well as in the development of the sensory lateral line in aquatic vertebrates (Ghysen and Dambly-Chaudiere, 2004). In all of these cases, groups of cells migrate as tightly associated epithelial sheets or clusters (e.g., *Drosophila* border cells and zebrafish lateral line primordium), or they possess a mesenchymal character as during gastrulation and neural crest migration. Because of its broad multicontextual and multiphylletic distribution, understanding cell migration in its various manifestations *in vivo* is likely to yield new insights into both the function and malfunction of key embryonic and postembryonic events. In this review, we will provide a succinct phenotypic description of several important model systems utilized to study cell migration *in vivo*. More importantly, we will highlight, compare and integrate recent advances in our understanding of how cell migration is regulated in these varied model systems.

In vivo models of cell migration

Because of the many known manifestations of developmental cell migration, a broad spectrum of model systems has been utilized to functionally dissect this process. Cells can migrate either individually or collectively as cohesive clusters, sheets or chains. Below we summarize experimental results obtained from several of the most intensively studied examples of developmental cell migration and attempt to find general mechanisms shared between the different models. Special emphasis is placed on the regulation of three crucial steps of morphogenic cell migration: (1) How a cell or a group of cells first becomes motile and detaches from its tissue of origin. (2) How cells are guided toward target sites. (3) How cells ultimately stop

* Corresponding author. Fax: +1 801 581 4233.
E-mail address: piotrowski@neuro.utah.edu (T. Piotrowski).

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migrating at the location where they are required for biological function (Fig. 1). Regulation of these three steps is detailed for several prominent models of morphogenic migration and compared in an effort to find general principles illustrated by multiple model systems.

Primordial germ cells: A model of individual cell migration during development

In vivo single cell migration has been extensively analyzed and modeled by studying cells of the immune system. The migratory behaviors of polymorphonuclear neutrophils from circulating blood to sites of infection or inflammation are well-known and have recently been reviewed (Cvejic et al., 2008). Migration of adult hematopoietic stem cells from the bone marrow into circulation and back to the marrow has also received its share of attention (Wright et al., 2001). Mechanistically, however, the study of germ cell migration during development has profoundly informed the field of cell migration. *Drosophila*, mouse and zebrafish are all powerful animal models for the mechanistic study of germ cell migration. In all of these model systems, primordial germ cells (PGCs) migrate long distances from their site of specification to the location of the prospective gonads (Fig. 2A). While PGCs may migrate as clusters of cells in some species, in zebrafish PGCs do not migrate coordinately and no stable cell–cell contacts are established (Reichman-Fried et al., 2004). Zebrafish PGC migration is therefore considered a model for individual cell migration. *Drosophila* and mouse PGC migration has been comprehensively reviewed (Kunwar et al., 2006) and we will therefore focus on recent results obtained in the zebrafish.

In 2005, an *in vivo* study of zebrafish PGC migration and behavior characterized three phases of cell migration (Blaser et al., 2005). During phase one newly specified cells exhibit a simple morphology with no detectable protrusions (Fig. 1A). In phase two the cells start to form protrusions in all directions but are still immotile (Fig. 1B). The signals responsible for the transition from a newly formed, phase one, round PGC to a phase two cell with multiple cell protrusions are not known. However, knockdown of the gene encoding the vertebrate-specific RNA-binding protein 'Dead end' blocks the competence of PGCs to become polarized and motile (Raz and Reichman-Fried, 2006; Weidinger et al., 2003). 'Dead end' suppresses the function of inhibitory miRNAs that normally suppress germ cell specific protein expression (Kedde et al., 2007). Unfortunately, it is not yet known how 'Dead end' influences cell motility.

Directional information in the form of a secreted guidance molecule is responsible for the transition into phase three, wherein the cells polarize their protrusions in the direction of migration and actively migrate toward their target (Fig. 1C). Even though mouse, chick and zebrafish PGCs migrate through very different somatic tissues, they are all polarized and guided by Cxcl12a–Cxcr4b chemokine signaling (Doitsidou et al., 2002; Knaut et al., 2003; Molyneaux et al., 2003; Stebler et al., 2004). Zebrafish PGCs express the chemokine receptor *cxcr4b* and surrounding somatic cells express variable levels of the ligand *cxcl12a* (Fig. 2A). Cxcl12a–Cxcr4b signaling is thought to lead to asymmetric calcium signaling within a PGC that induces directional orientation of cellular extensions toward the higher concentration of chemokine (Blaser et al., 2006).

Interestingly, Blaser et al. revealed that protrusions form in a non-directed fashion long before the PGCs become motile and before they are able to respond to the chemoattractant Cxcl12a. Additionally, early expression of Cxcl12a is incapable of causing premature PGC migration (Blaser et al., 2005). Thus, protrusion formation is not chemokine-dependent. The PGC maturation process occurs cell-autonomously, as older PGCs transplanted into younger host embryos start to migrate and reach the presumptive gonads before the endogenous PGCs do. These findings demonstrate that the regulatory interactions that lead to the acquisition of cellular protrusions necessary for migration can be distinct from the signals that ultimately guide a migrating cell toward its target. As we will see, this is a principle widely applicable to most, but not all well studied examples of cell migration during development.

Recently, an elegant study by Boldajipour et al. has demonstrated that, in addition to *cxcr4b*, a second chemokine receptor, called *cxcr7b*, is required for germ cell migration (Boldajipour et al., 2008). Unlike *cxcr4b*, *cxcr7b* is not expressed by the migrating PGCs. Rather, this receptor is expressed broadly in somatic tissues surrounding the migrating cells. A series of experiments involving expression of functional fluorescent fusion proteins demonstrated that somatically expressed Cxcr7b binds and internalizes Cxcl12a, thereby removing it

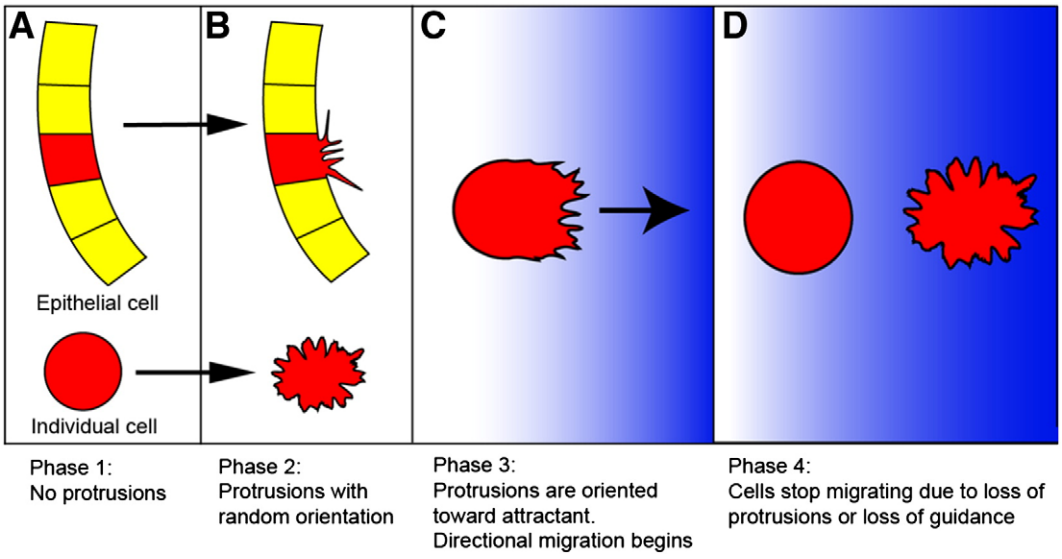

Fig. 1. Three steps of cell migration. (A) Prior to migration, cells exhibit a simple morphology and lack protrusions. This is true whether the premigratory cells are part of an epithelium (top) or individual cells (bottom). (B) In the first step of migration, a cell or group of cells (red) begins to elaborate cellular extensions preceding detachment from an epithelium (yellow). Note that a cell of non-epithelial origin, such as zebrafish PGCs, will not need to detach (bottom). In either case, cellular extensions are not initially polarized. Rather, cells extend protrusions in all directions but are still immotile. (C) Cellular extensions are polarized in the direction of migration in response to a gradient of chemoattractant, usually chemokine or growth factor ligands (blue). Cells may also be oriented by repulsive cues (not shown). (D) Cells stop migrating when they lose the ability to elaborate extensions (left) or they reach a region of uniform attractant (left).

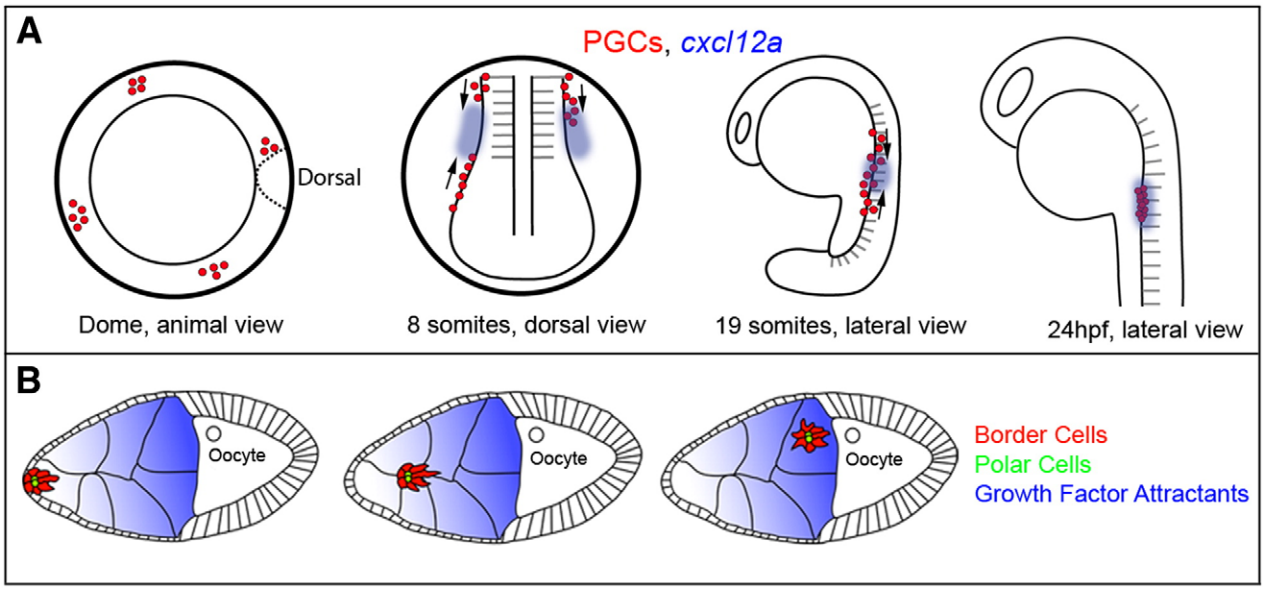

Fig. 2. Examples of *in vivo* cell migration models. (A) Different stages of primordial germ cell (PGC) migration in zebrafish (modified after Raz, 2003). Schematic drawings of embryos from dome stage to 24 hpf, which show the positions and movements of PGC clusters. PGCs are represented by small red circles. Arrows indicate the direction of migration. Blue shaded areas mark the expression of the chemoattracant *cxcl12a*. (B) Schematic cross sections through a *Drosophila* egg chamber during border cell migration. Actively migrating border cells (red) form at the anterior pole of the *Drosophila* egg chamber in response to JAK/STAT signaling from the non-motile polar cells (green). The border cells produce cellular extensions toward the oocyte that depend on gradients of multiple, redundant growth factor ligands (blue) in addition to PCP and Notch signaling (not shown). As border cells approach the oocyte, they occupy a region of uniform growth factor concentration where the cluster loses polarization of protrusions. Subsequently, the border cell cluster stops migrating and forms the micropyle organ to allow sperm entry and fertilization of the egg (not shown).

from extracellular space. This conclusion was confirmed by the demonstration that Cxcr7b expressing cells reduce the concentration of Cxcl12a in culture medium *in vitro*. Cxcr7b also limits the amount of Cxcl12a available for binding to Cxcr4b in PGCs *in vivo*, thus shaping a Cxcl12a protein gradient that is necessary to guide the cells toward the presumptive gonad. Consequently, knockdown of *cxcr7b* results in a dispersed pattern of PGCs, a phenotype similar to the one observed after overexpression of *cxcl12a*. Consistent with this role for somatically expressed *cxcr7b*, the *cxcr7b* loss of function phenotype can be partially rescued by a partial loss of *cxcl12a*. In summary, these experiments revealed that in PGCs the Cxcl12a gradient is not generated by a standing source of passively diffusing ligand but rather via posttranslational regulation of Cxcl12a (internalization and destruction of Cxcl12a by surrounding cells).

PGCs stop migrating upon reaching a region of uniform Cxcl12a expression. Such a region exists at the site of the prospective gonad (Fig. 1D; Doitsidou et al., 2002). Also, ectopic expression of Cxcl12a is capable of trapping PGCs in islands of high expression. Live imaging of stopping PGCs revealed that they still form protrusions as they stall. However, these protrusions lose polarity and further directed migration is inhibited (Reichman-Fried et al., 2004). Therefore, PGCs stop at their target destination due to a loss of directional information rather than a loss of motility. Uniform expression of guidance molecules is likely a general mechanism for stopping migrating cells at their target tissues, as will be seen in the discussion of other developmental models of migration below.

Border cells: A genetic model of collective migration

In the *Drosophila* egg chamber a group of cells migrates towards the posterior and then dorsal side of the oocyte where they contribute to the formation of the micropyle, which allows sperm entry and fertilization (Fig. 2B). This group of cells is called the border cell cluster and consists of two cell types, the border and polar cells (Montell et al., 1992). The border cell cluster is specified at the anterior pole of the egg chamber (Fig. 2B). To reach their final destination close to the oocyte, the 4–8 border cells and a pair of polar cells detach from the surrounding follicle cells and migrate posteriorly in between and along 15 large nurse cells (Fig. 2B). The polar cells are non-motile and are surrounded by the border cells, which elaborate long cellular extensions and provide the force for motility. Because the border cell cluster stays cohesive throughout its migration, it is considered a model for collective cell migration. The power of *Drosophila* genetics has allowed screens for border cell migration-deficient mutants that revealed numerous genes affecting almost every step in border cell specification, onset of migration and directed migration (Montell, 2001; Montell, 2003; Rorth, 2002). Therefore, border cell migration is by far among the best-understood models of collective cell migration.

Border cell protrusions are triggered by secretion of the cytokine-like ligand 'Unpaired' (Upd) from polar cells (Fig. 1B; Beccari et al., 2002; Ghiglione et al., 2002; Silver et al., 2005; Silver and Montell, 2001). Upd functions as a short range signal that leads to activation of the JAK/STAT signal transduction pathway and enables protrusion formation and detachment of follicle cells from the anterior pole of the egg chamber (Beccari et al., 2002; Silver and Montell, 2001). It has also recently been demonstrated that Notch signaling and core planar cell polarity (PCP) components are required for the acquisition of normal protrusive behavior (Bastock and Strutt, 2007; Prasad and Montell, 2007). Loss of Notch in border cells leads to fewer protrusions that are much longer lived suggesting defects in protrusion formation and dynamics (Prasad and Montell, 2007). Interfering with the core PCP pathway leads to a complete loss of actin rich protrusions (Bastock and Strutt, 2007). How these signaling pathways work together in regulating the complex and dynamic cell morphology that is necessary for subsequent migration has not been investigated. However, based on the strength of the STAT loss of function phenotypes and the pleiotropy of the STAT pathway, it is tempting to hypothesize that JAK/STAT signaling may be acting upstream of Notch and PCP activity.

JAK/STAT signaling in border cells continues to be activated during migration by sustained secretion of Upd from the polar cells. This activation is required for the maintenance of protrusions and sustained motility (Silver et al., 2005). In rare cases where individual

wild-type border cells lose contact with the polar cells, the detached border cells immediately lose protrusions and cease migration (Prasad and Montell, 2007). Interestingly, ectopic expressions of Upd or mutations that activate the JAK/STAT pathway induce migration of usually non-motile follicle cells. These ectopically migrating follicle cells migrate individually or as differently sized clusters, suggesting that border cell cohesiveness is due to sustained requirement for Upd production by polar cells (Silver et al., 2005; Silver and Montell, 2001).

Detachment of the border cell cluster from follicle cells (Fig. 1B) relies on the classical apico-basal polarity machinery defined by interactions between Par-1 at basolateral membranes and Par-3/aPKC at apical membranes. Loss of Par-1 function in border cells causes a strong defect in detachment and an associated loss of Par-3 localization. Additionally, overexpression of a non-localizable allele of Par-3 leads to the failure of border cell detachment (McDonald et al., 2008). The apically localized Par-3/aPKC complex is required for formation and stabilization of E-cadherin-based adherens junctions (Chen and Macara, 2005; Hirose et al., 2002). During detachment, wild-type border cells reorganize E-cadherin from apically localized adherens junctions with neighboring follicle cells to broad basolateral domains between cells of the border cell cluster (McDonald et al., 2008). Mutations in the Par complex cause failure to reorganize these adherens junctions and therefore mutant cells are unable to detach. An interesting consequence of this reorganization is that the basal aspect of wild-type border cells in the migrating cluster faces the polar cells. Therefore, cells at the trailing edge of the cluster have the opposite orientation as cells at the leading edge (McDonald et al., 2008).

Additionally, although border cells deficient in Par-1 still extend protrusions, their directionality is lost and the undetached border cells extend more protrusions laterally along the follicle cells. Interestingly, the protrusion directionality defects were independent of Par-3 localization defects, as border cells expressing non-localizable Par-3 did not have such dramatic protrusion defects although they still fail to detach (McDonald et al., 2008). Therefore, Par-1 has at least two roles in early border cell migration: First, it must be present to polarize cells and reorganize adherens junctions enabling cluster detachment. Second, it is necessary for normal protrusive behavior via an unknown Par-3 independent mechanism.

For directed migration, border cell clusters do not utilize the chemokine signaling pathway but orient and migrate up a gradient of four functionally redundant growth factor ligands: Pvf1 (a PDGF/VEGF like factor), Spitz, Keren and Grk (Fig. 1C; Duchek et al., 2001; McDonald et al., 2006; McDonald et al., 2003). Pvf1, Grk, Spitz and Keren are produced in the oocyte at the time of migration and diffuse toward the anterior pole (Duchek et al., 2001; McDonald et al., 2006). These ligands bind to two partially redundant receptors, Pvr and Egfr, expressed in the border cells but not in the polar cells (Duchek et al., 2001; Wang et al., 2006).

The leading and trailing edges of individual cells, as well as cells occupying different positions within the cluster are exposed to different concentrations of chemoattractant growth factors. Two possible mechanisms exist by which the cluster orients in this gradient (Rorth, 2007). In the first mechanism individual cells mount different levels of non-localized signal transduction based on their position within the growth factor gradient. Comparisons between the levels of signaling in different cells then give the cluster directionality. In the second mechanism, individual cells respond independently and migrate towards a higher source of attractant by intracellular mechanisms that detect the highest level of attractant. In this scenario, asymmetry of attractant concentration across individual cells leads to localized accumulation of factors at the leading edge of the cell that are necessary for directional migration. Indeed, it has been shown that there is more intense growth factor signaling at the leading edges of individual cells in the border cell cluster and that disrupting this localization coincides with migration defects (Jekely et al., 2005). Of course, these two mechanisms are not mutually exclusive and may both be operating at the same time. For instance, asymmetric receptor activation across individual cells may polarize these cells toward the higher concentration of attractant and, simultaneously, differences in between the total levels of signaling within cells occupying different positions of the cluster might be polarizing the entire migrating tissue.

Live imaging experiments to observe the behavior of migrating border cells has allowed evaluation of these mechanisms. If cluster polarity is important for directional migration then this polarity should be stable and the border cells will not shift relative to other cells in the cluster during migration. On the other hand, if all the cells of the cluster are guided independently they should be free to exchange position within the cluster as it migrates. Early in migration, cells at the leading edge of the cluster maintain their position and extend much longer protrusions than other cells (Bianco et al., 2007). During this phase loss of growth factor receptors leads to increased protrusions from cells at the rear of the cluster (Prasad and Montell, 2007). Because the border cells are polarized outward with their basolateral domains facing the centrally located polar cells, protrusions from cells at the trailing edge of the cluster generate force in the opposite direction of normal migration impeding forward progress of the cluster. Therefore, some presently unknown growth factor-dependent mechanism is necessary to limit the protrusiveness of trailing edge cells (Prasad and Montell, 2007). Because cells do not exchange positions within the cluster and cells at the leading edge exhibit different behavior from those at the trailing edge, cluster polarity appears to be important during this early phase of border cell migration.

As migration continues, however, cells in the cluster begin to constantly exchange positions (Bianco et al., 2007). Therefore, stable cluster polarity plays a minor role in guiding directional migration at these later stages. As the cluster enters a region of higher growth factor concentration, an individual cell chemotaxis mechanism becomes more prevalent. Supportive evidence for this finding is that slight overexpression of growth factor attractant that presumably preserves its gradient speeds the transition to individual cell chemotaxis. Availability of more growth factor causes individual migrating cells to exchange positions within the cluster prematurely (Bianco et al., 2007).

Upon reaching the oocyte, border cell protrusions become non-polarized and migration ceases, although formation and extension of undirected extensions may go on for some time afterwards (Prasad and Montell, 2007). Similar to PGCs, this stalling is likely due to the cells occupying a region of uniform chemoattractant and therefore losing guidance information. Consistent with this interpretation, drastic overexpression of growth factor chemoattractants throughout the egg chamber that abolishes the gradient also abolishes directional migration, even though the cells are still protrusive but unpolarized (McDonald et al., 2006).

The posterior lateral line: A vertebrate model of collective migration

Cranial placodes are transient embryonic structures that give rise to a variety of sensory organs and ganglia in non-mammalian and mammalian vertebrates (Schlosser, 2006; Schlosser and Northcutt, 2000). Cranial placodes are specified in the vertebrate head in a pan-placodal horseshoe-shaped region (Schlosser, 2006). Although placodal tissues are specified in a single broad location, they eventually occupy locations distributed along the head and, in the case of the posterior lateral line placode of aquatic vertebrates, along the entire anterior–posterior axis of the animal. This distribution is achieved by subdivision of the pan-placodal field into separate placodes and subsequent migration of placodally derived cells to the locations in which they are required to differentiate in order to establish normal

sensory or secretory function. The development of the sensory lateral line system of aquatic vertebrates has emerged as a powerful model to investigate placode migration. The lateral line system is composed of a series of mechanosensory organs (neuromasts) in the skin of the animal (Fig. 3A, yellow spots). Neuromasts contain hair cells that sense water motion and enable the animal to orient, socialize and forage. All cells of the lateral line are derived from migrating cranial placodes (Fig. 3B). Primitive ray-finned fish, such as the actinopterygian *Polypterus*, possess six embryonic lateral line placodes that give rise to several lines on the head and the trunk (Fig. 3C; Piotrowski and Northcutt, 1996). In teleosts, such as the zebrafish the placodal field subdivides into only an anterior and a posterior lateral line placode. The posterior lateral line placode (hereafter referred to as the primordium) migrates from behind the ear to the tail tip as a compact cluster of approximately 100 cells, periodically depositing clusters of cells that subsequently form sensory organs (Fig. 3D; Metcalfe et al., 1985). All cells of the migrating cluster extend protrusions in the direction of migration. Extensions from cells occupying the leading edge of the cluster are readily apparent, while extensions from more trailing cells extend underneath the cells in front of them and require mosaic labeling to observe (Haas and Gilmour, 2006).

In contrast to *Drosophila* border cells, the posterior lateral line placode differs in one important aspect of how it migrates collectively. The posterior lateral line placode moves as a tight cluster of cells that rarely exchange relative positions during migration, whereas border cells adhere only loosely to each other and exchange positions frequently. Here we focus on the significant progress that has been made in our understanding of collectively migrating cells using the zebrafish posterior lateral line cells as a model system.

The posterior lateral line primordium is specified at the extreme posterior tip of the pan-placodal region in zebrafish embryos (Kozlowski et al., 1997). Cells in the premigratory primordium begin extending protrusions in all directions and exhibit tumbling motility by 18 hours post-fertilization (hpf; AA and TP, unpublished observations). Around 22 hpf protrusions of primordium cells become oriented and the cluster begins migrating posteriorly (Sapede et al., 2002). It is presently not known what triggers the onset of motility in the posterior lateral line primordium. The premigratory primordium begins to express *cxcr4b* at the same time when cells begin to tumble (18 hpf), which suggests that chemokine signaling might trigger the formation of protrusions. However, embryos in which the *cxcl12a* guidance molecule (see below) or its receptors in the primordium are mutated or inhibited, still possess protrusions and are quite capable of undirected tumbling motility (Aman and Piotrowski, 2008; Haas and Gilmour, 2006). This is similar to PGCs where lack of *cxcl12a* does not impair protrusion formation and tumbling motility (Blaser et al., 2005). Although numerous mutations and manipulations cause primordium stalling, none of these have been able to abolish motility (tumbling) of individual cells within the tissue. It remains to be tested whether, in analogy to the roles of JAK/STAT and PCP signaling in *Drosophila* border cells, the STAT or PCP pathway is required for the onset and maintenance of motility of the posterior lateral line primordium.

Similar to PGCs, Cxcr4b–Cxcl12a chemokine signaling is the major chemoattractive system in the posterior lateral line primordium (David et al., 2002; Li and Kuwada, 2004). *cxcl12a* is expressed in cells along the horizontal myoseptum prefiguring the track on which the posterior lateral line primordium migrates (Fig. 3D; blue stripe). Cxcl12a is necessary for directing cell protrusions toward the tail of the embryo, as loss of *cxcl12a* leads to non-directed, random protrusion formation (Haas and Gilmour, 2006). In contrast to border cell migration, the gradient of chemoattractant is not due to passive

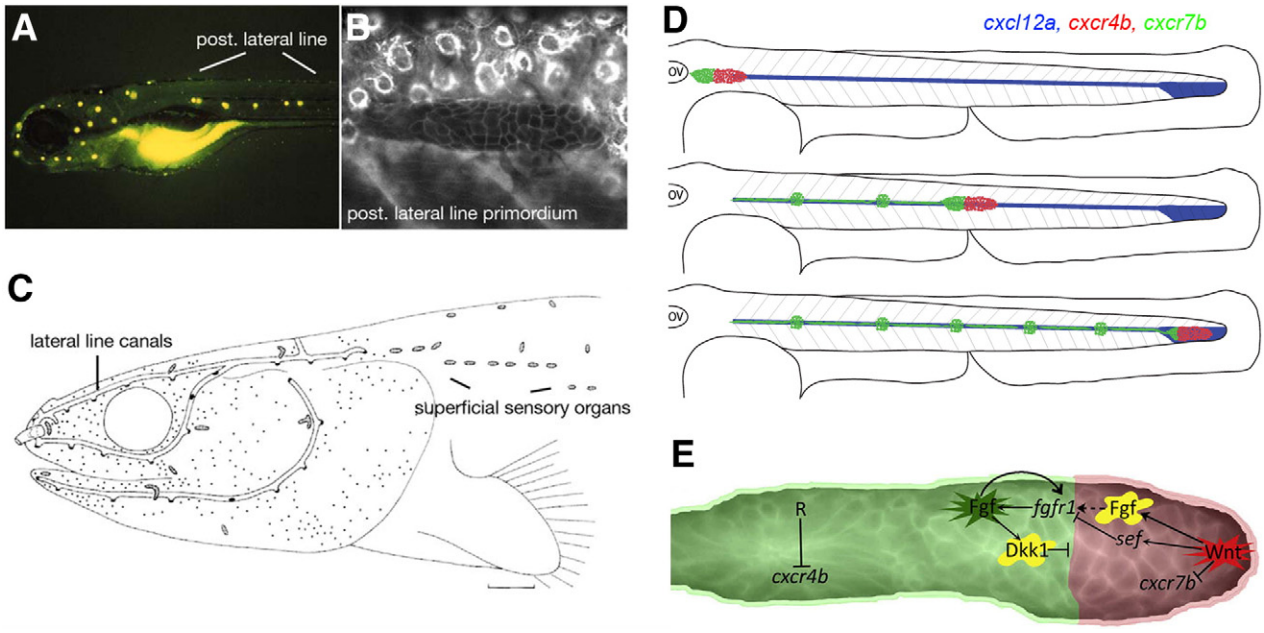

Fig. 3. The zebrafish sensory lateral line system. (A) The fluorescent vital dye DASPEI labels hair cells in the zebrafish lateral line sensory organs. The sensory organs are arranged in lines around the eye and on the trunk. (B) The posterior lateral line placode/primordium migrates as a tight cluster of cells from the ear to the tail tip periodically depositing pro-sensory organs. (C) Schematic drawing of the lateral line system in the primitive ray-finned fish *Polypterus* (modified with permission from *Brain Behavior and Evolution*). Sensory organs are either situated in bony canals and are connected to the environment via openings or they are located superficially in the skin (gray patches). (D) Schematic representation of primordium migration and sensory organ deposition. The zebrafish lateral line primordium forms just posterior to the otic vesicle (OV) and migrates along a uniform stripe of *cxcl12a* attractant (blue). The migrating lateral line primordium expresses two Cxcl12a binding receptors: *cxcr4a* (red) is expressed in the leading portion of the migrating tissue and is the receptor necessary for guidance toward the tail-tip. *cxcr7b* (green) may not signal in response to Cxcl12a binding and likely is responsible for shaping a gradient of Cxcl12a protein across the length of the primordium. As the primordium migrates, it deposits a series of sensory organ progenitors along the side of the embryo (green rosettes). (E) Cell signaling interaction within the primordium responsible for maintenance of chemokine receptor asymmetry. Solid lines denote genetic interactions and dashed lined denote protein diffusion. Wnt/β-catenin pathway activation in the leading zone (red) leads to Fgf pathway activation in the trailing zone (green). Exclusivity of these domains is maintained by the induction of *dkk1* by Fgf signaling in trailing cells and induction of *sef* by Wnt/β-catenin signaling in leading cells. *cxcr7b* expression in leading cells is inhibited by Wnt/β-catenin signaling, and *cxcr4b* expression is restricted from the trailing zone via the activity of an uncharacterized repressor (R) that is inhibited if Wnt/β-catenin signaling is active throughout the primordium.

diffusion from a source of ligand at the migration target. Rather, *cxcl12a* mRNA is present in a uniform stripe along the prospective migratory path (David et al., 2002). Although a Cxcl12a protein gradient spanning the AP axis has not been ruled out, genetic experiments show that the primordium is capable of migrating in either direction along the uniform stripe of *cxcl12a* mRNA. For example, in N-cadherin mutants, in which somites and the horizontal myoseptum are partially disrupted, the primordium occasionally performs a U-turn (Kerstetter et al., 2004).

Two receptors for Cxcl12a are expressed in the primordium. *cxcr4b* is expressed broadly in the leading portion of the primordium and *cxcr7b* is only expressed in about the trailing one third of the tissue (Fig. 3D; Dambly-Chaudiere et al., 2007; David et al., 2002; Valentin et al., 2007). In the absence of a simple, diffusion based Cxcl12a gradient, this primordium polarization itself is likely the key mechanism allowing directional migration (Dambly-Chaudiere et al., 2007, Valentin et al., 2007). Chemokine receptor asymmetry is crucial for directional migration, as loss of either receptor leads to stalling of the tissue. Similarly to what has been observed in chemoattractant deficient PGCs and border cells, loss of directional migration does not lead to a loss of cell motility but cells migrate along random independent vectors effectively abolishing correct directional migration (Aman and Piotrowski, 2008; Dambly-Chaudiere et al., 2007; Doitsidou et al., 2002; Haas and Gilmour, 2006; Prasad and Montell, 2007). In analogy to PGCs, an attractive hypothesis is that that Cxcr7b receptors expressed in trailing cells of the primordium function as a Cxcl12a sink to reduce the concentration of Cxcl12a available for Cxcr4b binding. Cxcl12a sequestration by Cxcr7b possibly leads to the formation of a dynamic Cxcl12a protein gradient across the primordium enabling directional migration on a uniform stripe of Cxcl12a (Aman and piotrowski, 2009; Dambly-Chaudiere et al., 2007; Valentin et al., 2007). This mechanism also explains why in certain experimental contexts the primordium can turn and migrate in the opposite direction along the *cxcl12a* stripe. As long as primordium polarity is maintained, a dynamic gradient of Cxcl12a protein can be produced by the migrating primordium itself.

The significance of primordium polarity for directed migration raises the question of what mechanisms initiate and maintain this polarity. Primordium polarization, and thus chemokine receptor asymmetry, is maintained by a paracrine feedback mechanism involving asymmetric Wnt/β-catenin and Fgf pathway activation (Fig. 3E; Aman and Piotrowski, 2008). Activation of Wnt/β-catenin signaling in cells occupying the leading portion of the cluster leads to expression of secreted Fgf ligands. However, Wnt/β-catenin pathway activation simultaneously upregulates the membrane-bound Fgf pathway inhibitor *sef* preventing Fgf pathway activation in leading cells. As Fgf ligands are free to diffuse out of this inhibitory domain, they stimulate expression of target genes in the trailing portion of the tissue. Fgf signaling, in turn, restricts Wnt/β-catenin target genes to the leading zone by inducing *dkk1* expression in trailing cells. Wnt/β-catenin inhibits *cxcr7b* in leading cells and promotes *cxcr4b* expression by inhibiting an unidentified repressor of *cxcr4b*. Thus, the reciprocal interactions between Wnt/β-catenin and Fgf signaling are critical to maintain polarized expression of the chemokine receptors *cxcr4b* and *cxcr7b* and for sustained directional collective migration (Fig. 3E).

Even though we understand how primordium polarity is maintained, it remains enigmatic how primordium polarity is initially established after placode induction. Chemokine signaling polarizes cells in multiple systems, making it an attractive candidate signaling pathway possibly involved in polarizing the lateral line primordium. However, primordium polarity forms normally in the absence of Cxcl12a (Aman and Piotrowski, 2008). Also, the Wnt ligand has not been identified yet. Thus, the Wnt signal could be provided by the environment or it could be produced by cells at the leading edge. In this second scenario primordium polarity is maintained and reinforced by signaling interactions between the cells of the cluster without requiring input from the underlying tissues.

A mechanism by which collectively migrating cells express different genes in the leading and trailing regions could have implications for collective cancer invasion. Small differences in gene expression among tumor cells might be reinforced by paracrine feedback loops leading to cluster polarization and onset of migration and invasion. Also, if cluster polarity indeed maintains itself in the absence of signals from surrounding tissues, this could explain why groups of cancer cells are able to migrate through very diverse tissues. Interestingly, the leading cells of invasive cancer collectives express high levels of matrix remodeling enzymes, including Mmp14, which are targets of Wnt/β-catenin signaling in colorectal adenoma (Benini et al., 2005). The role of Wnt/β-catenin signaling in polarizing collectively migrating invasive tumors has not been evaluated.

It is still enigmatic how the posterior lateral line primordium stops migration at the tail tip. It is possible that, similar to stalling PGCs and border cells, the primordium encounters a region of uniform chemoattractant in this region. Indeed, *cxcl12a* mRNA is expressed much more broadly in the tail tip than along the horizontal myoseptum (Fig. 3D). However, it is unclear whether this mechanism is sufficient to stop the primordium as *cxcr7b* expression in cells at the rear of the primordium generates a dynamic Cxcl12a gradient. It is also possible that upon reaching the tail tip, chemokine independent signals cause the primordium to lose protrusions and differentiate as neuromasts. Live imaging and gene expression analysis of primordia as they reach the tail tip and cease forward migration is required to shed light on this question.

Angiogenic sprouting: Collective migration of thin cellular filaments

Angiogenic sprouting in vertebrates is defined as the formation of new blood vessels from existing vessels. During embryonic and postnatal development, networks of blood vessels undergo significant remodeling and elaboration in order to completely perfuse tissues ensuring an adequate blood supply. Angiogenic sprouting is one of the major mechanisms used to remodel and elaborate vessel networks. This review will briefly focus on regulation of sprout collective migration in the postnatal mouse retina to allow comparisons with other models of migration (Figs. 4A, A′). Angiogenic sprouts are composed of a single tip cell followed by a variable number of stalk cells. As these cells remain tightly adhered to each other during migration, this process is considered an example of collective cell migration. However, it is distinct from the collective cell migration of the border cell cluster and the posterior lateral line primordium. The sprout remains attached to the parent vessel and is generally a thin filament of cells rather than a cluster of cells (Fig. 4A′).

The mouse retina has proven to be a potent model for elucidating mechanism of endothelial cell migration during angiogenesis. Angiogenesis occurs in the mouse retina after birth and involves the formation of an elaborate vascular network from a simple capillary ring formed at the center of the embryonic retina. Sprouts emerge from these vessels and migrate toward the periphery of the retina, branching and proliferating as they go leading to the formation of a complicated network of highly branched vessels (Fig. 4A; for comprehensive reviews of the mouse retina angiogenesis model see Fruttiger, 2007; Gerhardt, 2008; Uemura et al., 2006).

The first step in angiogenic sprouting is the specification of a highly motile tip cell from among quiescent endothelial cells of an existing blood vessel. In the mouse retina VEGF-A is necessary and sufficient for the specification of tip cells (Gerhardt et al., 2003). The tip cell upregulates Delta ligands, such as Dll4 in retinal sprouts, which subsequently signal through Notch receptors present throughout the quiescent vessel to limit the acquisition of tip cell fate to a few cells. Migrating cells in the rest of the sprout specified by the action of

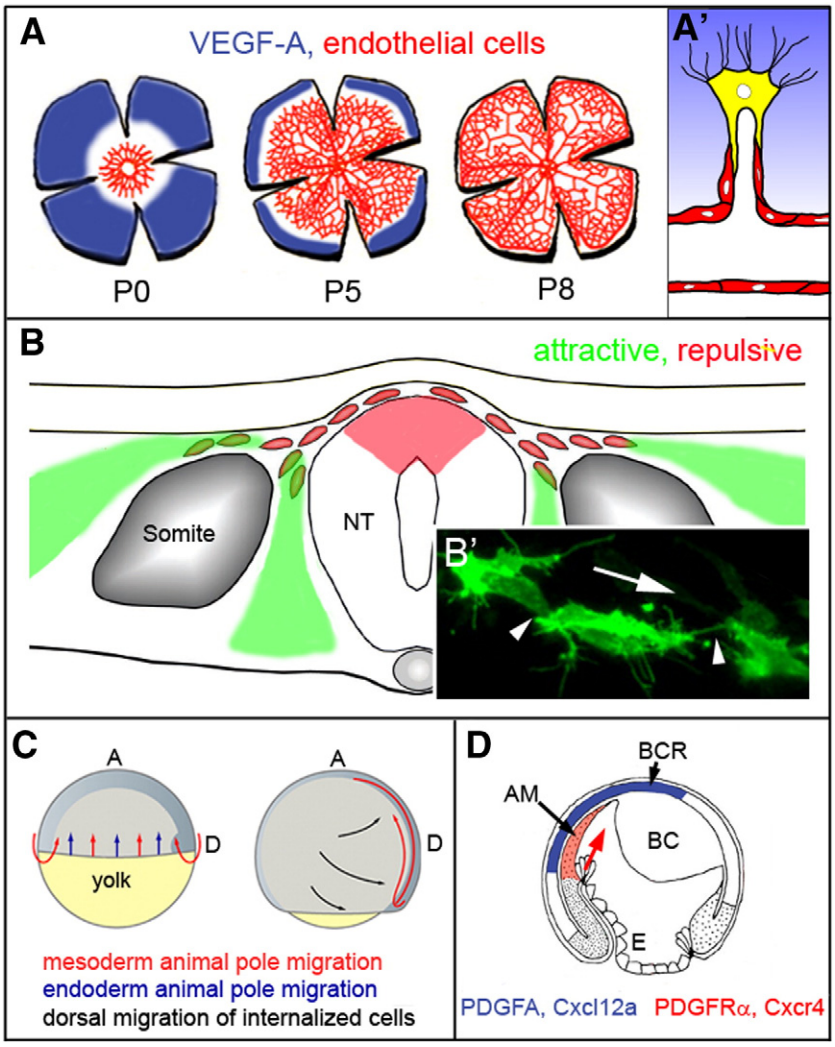

Fig. 4. Migration of angiogenic sprouts, neural crest cells and cells during zebrafish gastrulation. (A) Schematic presentation of retinal angiogenesis in the mouse from perinatal days 1 to 8 (P1 to P8). Sprouting vessels (red) migrate from the central retina toward VEGF-A (blue) expressed in the peripheral retina. Migration occurs concomitantly with endothelial cell proliferation and vessel branching leading to a complex vascular network that covers the entire retina. (A′) Schematic of an individual angiogenic sprout migrating up a VEGF-A gradient. Note that only the tip cell (yellow) extends lammelipodia (modified from Gerhardt et al., 2003). (B) Schematic cross section through the trunk of a vertebrate embryo during neural crest migration. Neural crest cells undergo EMT, delaminate from the neural tube and then migrate ventrally along different paths in response to attractive cues (green) and repulsive cues (red) (modified from Taneyhill, 2008). (B′) High resolution image of GFP labeled migrating neural crest cells *in vivo* connected by thin lamellipodia (arrow heads). Arrow denotes direction of stream migration (modified from Rupp and Kulesa, 2007). (C) Schematic representation of gastrulation movements in zebrafish. (Left) Shield stage. Presumptive mesoderm cells at the margin internalize and actively migrate toward the animal pole (red arrows). While the mesoderm migrates directionally the endoderm spreads towards the animal pole via a random walk (blue arrows). These migrations occur across the entire circumference of the blastoderm. (Right) 90% epiboly stage. Internalization and migration of mesoderm continues. Internalized mesoderm and endoderm cells directionally migrate and intercalate dorsally, contributing to convergent extension (black arrows; reproduced from Shier and Talbot, 2005; A = Animal pole, D = Dorsal). (D) Cross section through a *Xenopus* embryo midway through gastrulation. The anterior mesendoderm (AM) expresses PDGFRα and Cxcr4 (red) and migrates toward the blastocoel roof (BCR) in response to the guidance molecules PDGFA and Cxcl12a (blue). Red arrow shows the direction of migration. Abbreviations: BC = Blastocoel, E = Endoderm (modified from Winklbauer et al., 1996).

Delta-Notch signaling from the tip are known as stalk cells (Claxton and Fruttiger, 2004; Hellström et al., 2007; Krebs et al., 2000). Stalk cells do not form elaborate protrusions like tip cells and may not actively contribute force for motility to the elongating sprout (Fig. 4A′; Gerhardt et al., 2003).

Once specified by VEGF-A, tip cells orient and migrate from the central retina toward the peripheral retina which expresses higher levels of VEGF-A, causing radial growth of the vascular plexus (Fig. 4A). As the retina matures, VEGF-A production is stimulated by local hypoxia ensuring that vascular sprouts grow into regions that require increased vascular coverage (Stone et al., 1995). The result of this process is a highly branched network of blood vessels that entirely perfuses the retina. In contrast to the examples discussed above, onset of motility and directed migration are regulated by the same signaling molecule, VEGF-A. This ligand is capable of both stimulating protrusions in nascent tip cells and orienting these protrusions toward their targets. A unique feature of angiogenic sprouts is that they stop migrating because they induce downregulation of their chemoattractant VEGF-A. As sprouts migrate into regions of local hypoxia and begin delivering blood to these tissues, hypoxia is relieved and VEGF-A expression subsides (Stone et al., 1995). Therefore, in contrast to border cells and PGCs, which stop migrating upon reaching a region of uniform chemoattractant, angiogenic sprouts stop migrating due to a loss of protrusions caused by a downregulation of chemoattractant.

Interestingly, the VEGF-A isoforms produced in the retina bind tightly to heparin components of the ECM secreted by retinal astrocytes, which forms a functional VEGF-A protein gradient. Therefore, over-expressing VEGF-A or expressing a non-heparin binding isoform of VEGF-A destroys the gradient and causes impaired sprout migration

(Gerhardt et al., 2003). Thus, a general feature of *in vivo* cell migration is the requirement for post-translational regulation of chemoattractant ligands to generate gradients in extracellular space.

Neural crest migration: Collective migration of cellular streams

Neural crest cells have been a classical model to study cell migration *in vivo* (Le Douarin, 2004). Neural crest cells arise along the border between neural and non-neural ectoderm. These cells subsequently delaminate from the dorsal neural tube and migrate throughout the embryo to give rise to neural, as well as non-neural tissues (Fig. 4B; Knecht and Bronner-Fraser, 2002). Once they reach their respective targets, neural crest cells differentiate into cartilage, pigment cells, sensory neurons, ganglia and contribute cells to the sympatho-adrenal glands. At a gross morphological level neural crest cells appear to migrate in loosely associated chains, however scanning electron micrographs and live imaging have demonstrated that cells communicate via fillipodia and that cell–cell communication is crucial for directed migration (Fig. 4B′; Bancroft and Bellairs, 1976; Davis and Trinkhaus, 1981; Teddy and Kulesa, 2004).

Neural crest cells form in dorsolateral regions of the neural tube and, as they begin to migrate, undergo an epithelial to mesenchymal transition (EMT). EMT is triggered by several signaling pathways, chiefly BMP, FGF and WNT (reviewed in Acloque, 2009). Downstream of these signaling pathways, transcription factors such as Snail and Foxd3 that modulate cell–cell adhesion and cell polarity are activated and thus enable cells to leave the neural epithelium. For example, the zinc-finger transcription factor Snail represses E-cadherin, which in turn is crucial for modulating adherens junctions (Nieto, 2002). Snail also acts as a repressor of genes regulating tight junction proteins or proteins involved in the establishment of apico-basal polarity (reviewed in Acloque, 2009; Ikenouchi et al., 2003; Peinado et al., 2007). Interestingly, a recent study demonstrated that the cell-adhesion molecule Cadherin-11 not only affects neural crest cell adhesion but also directly promotes migration (Kashef et al., 2009). Cadherin-11 regulates fillipodia and lamellipodia formation via guanine nucleotide exchange factor (GEF)-Trio and the small Rho GTPases (Jaffe and Hall, 2005). Thus, cell adhesion molecules play multiple important roles in the regulation of migration, which have to be tested in other model systems.

So far, all well-described guidance molecules involved in neural crest cell migration are repulsive in nature. Among these are the ligand receptor pairs Robo/Slit, Neuropilin/Semaphorin and Ephrins/Eph (reviewed in Kuriyama and Mayor, 2008). Especially, the non-canonical Wnt/planar cell polarity (PCP) pathway is essential for directional migration of neural crest cells. The PCP pathway stabilizes protrusions and in its absence, protrusions form in a non-directed fashion (De Calisto et al., 2005). Importantly, the PCP pathway is responsible for contact inhibition. As cells touch each other, the PCP pathway is locally activated at zones of contact leading to activation of RhoA and collapse of cell protrusions (Carmona-Fontaine et al., 2008). Thus, leading cells are repelled by follower cells causing efficient directed migration. However, even though contact inhibition surely plays an important role, it does not exclude the possibility that attractive chemokine signaling is also involved in guiding neural crest migration. In support of an involvement of chemotaxis Cxcl12 promotes migration of cultured neural crest-derived dorsal root ganglion cells and *cxcr4a* and *cxcl12a* are expressed in the zebrafish pharyngeal arches, possibly guiding cranial neural crest cells (Belmadani et al., 2005; Thisse et al., 2001).

Neural crest cells stop migrating in areas where repulsive signals are low. For example, trunk neural crest cells migrate away from the neural tube to form sympathetic ganglia ventral of the somites. Cranial neural crest cells coalesce into ganglia by integrating repulsive signals such as Ephrin/Eph in interganglionic regions and attractive cues, such as N-cadherin (Kasemeier-Kulesa et al., 2006).

Vertebrate gastrulation

Gastrulation movements are driven by several mechanisms such as polarized planar and radial intercalations, cell shape changes, and active cell migration (Fig. 4C; Keller, 2005; Rohde and Heisenberg, 2007; Solnica-Krezel, 2005). For instance, *Xenopus* anterior mesendoderm actively migrates (Fig. 4D), whereas trunk mesodermal cells intercalate (not shown). Both processes are regulated by different molecular mechanisms exemplified by the fact that they respond differently to the activation of Rho-GTPases (Ren et al., 2006). Additionally, cells in different germ layers may utilize distinct migration strategies at the same developmental stage. For instance, early in zebrafish gastrulation mesodermal cells directionally migrate toward the animal pole while endodermal cells spread toward the animal pole by an active, non-directed random walk (Pézeron et al., 2008). The multitude of movements that govern gastrulation makes it difficult to define the steps characteristic of other models of cell migration (Fig. 1). Nevertheless, we would like to briefly summarize findings that have been made by studying gastrulation movements that have relevance to our understanding of cell migration in general.

Before mesodermal cells commence active migration they undergo EMT similar to neural crest cells. Studies in mice demonstrated that, during gastrulation, EMT is induced by Fgf which upregulates Snail. Snail, in turn, downregulates E-cadherin causing cells to acquire a mesenchymal character (Carver et al., 2001; Ciruna and Rossant, 2001). Studies in zebrafish identified an additional pathway that induces EMT via the activation of the transcription factor Stat3 and its downstream target LIV1 (Solnica-Krezel, 2005; Yamashita et al., 2002; Yamashita et al., 2004).

Similarly to neural crest cells, migrating dorsal mesodermal cells are of mesenchymal character that are loosely connected and extend many protrusions toward the direction of migration (Lawson and Schoenwolf, 2001; Ulrich et al., 2003; Winklbauer et al., 1996). Although they are only loosely connected, cells migrate as a coherent sheet that optimizes cell migration. Explant experiments have demonstrated that individual cells migrate more slowly than when they are part of a sheet of cells (Davidson et al., 2002; Ren et al., 2006). Similarly to posterior lateral line primordium migration, more posterior cells extend cell protrusions underneath the preceding cells (Winklbauer and Nagel, 1991; Winklbauer and Selchow, 1992). In contrast, zebrafish endoderm cells initially migrate as isolated individuals with no interactions between the migrating cells (Pézeron et al., 2008).

In *Xenopus*, anterior mesendoderm cells are guided toward the blastocoel roof by the growth factor PDGFA (Fig. 4D). Interestingly PDGFA is not required for mesendoderm protrusions and motility. Therefore, loss of PDGFA results in randomized migration of mesendoderm cells (Nagel et al., 2004). This is similar to the role of chemoattractant guidance molecules in PGCs, border cells, and the lateral line primordium. Additionally, during *Xenopus* gastrulation, *cxcl12a* is expressed in cells of the blastocoel roof and *cxcr4* is expressed in the leading edge of the migrating anterior mesendoderm (Fig. 4D; Fukui et al., 2007). Overexpression or knockdown of *cxcl12a* severely impairs migration demonstrating a role for chemokine signaling in mesendoderm migration. Explant experiments show that mesendoderm cells migrate toward blastocoel roof cells *in vitro* and that this migration requires chemokine signaling, as no migration occurs unless the blastocoel roof explants express *cxcl12a* and the mesendoderm explants expresses *cxcr4* (Fukui et al., 2007).

In zebrafish, early endoderm migration toward the animal pole occurs via an undirected random walk that serves to evenly populate the inner surface of the blastoderm with cells, whereas later migration toward the dorsal side of the embryo relies on directional migration (Fig. 4C, black arrows; Pézeron et al., 2008). Two studies revealed that chemokine signaling is essential for the later dorsal migration of endoderm (Mizoguchi et al., 2008; Nair and Schilling, 2008). *cxcr4a* is expressed in the endoderm, whereas the ligands *cxcl12b* and *cxcl12a*

are expressed in the mesoderm along which the endoderm migrates. In the absence of *cxcr4a* or *cxcl12a*, the anterior endoderm is displaced and has defects in its dorsal migration, however, ectoderm and mesoderm migration is normal. The two groups came to different conclusions with regard to the underlying molecular mechanisms of the endoderm migration defect. Mizoguchi et al. concluded that chemokine signaling is important for guiding endodermal cells, whereas Nair and Schilling's data implies that chemokine signaling is crucial for Integrin mediated adhesion (discussed below).

Mizoguchi et al. (2008) characterized the phenotype of *cxcl12a/b* morphant embryos as a loss of chemotaxis as live imaging revealed that endodermal cells extend fewer protrusions and that these protrusions are not properly oriented along the direction of migration. Furthermore, in the absence of chemokine signaling, endodermal cells were observed to migrate with similar speed as endodermal cells in control embryos but their directionality was impaired. These data were interpreted to show that mesodermally expressed Cxcl12a/b is acting as a chemoattractant to guide the Cxcr4a expressing endoderm. In support of this conclusion, endodermal cells cluster around ectopic patches of *cxcl12a/b* in *cxcl12a/b* MO embryos (Mizoguchi et al., 2008).

Over the past few years it has become increasingly clear that, in addition to guidance cues, cell adhesion molecules play an essential role in regulating gastrulation movements (Hammerschmidt and Wedlich, 2008; Solnica-Krezel, 2006; Witzel et al., 2006). Epiboly movement and prechordal mesoderm migration depend on E-cadherin (Kane et al., 2005; Montero et al., 2005). Similarly to what has been described for Cadherin-11 function during neural crest migration, Fibronectin–Integrin interactions are not only essential for cell adhesion but also for lamellipodia formation (Hammerschmidt and Wedlich, 2008; Winklbauer and Keller, 1996), development of directed protrusions (Davidson et al., 2006), and cell polarity (Marsden and DeSimone, 2001).

Interestingly, chemokine signaling has also been demonstrated to control ECM-integrin-dependent adhesive interactions between the endoderm and the mesoderm by regulating *integrin* transcription in the endoderm (Nair and Schilling, 2008). This conclusion is supported by the finding that zebrafish *cxcr4a*-depleted cells adhere much less efficiently to Fibronectin-coated substrates and that the migration defect observed in *cxcr4a* morphant embryos can be rescued by injection of *integrin* (*itgb1b*) mRNA (Nair and Schilling, 2008). It is possible that the clustering of endoderm cells around ectopic *cxcl12a* observed by Mizoguchi et al. is also due to the regulation of integrin mediated adhesion rather than chemotaxis. In this interpretation, endoderm cells stop migrating on ectopic patches of *cxcl12a* expression due to strong adhesion to the Fibronectin-containing ECM that overlies them. Likewise, the defects in protrusion formation described by Mizoguchi et al. could be due to loss if integrin mediated adhesion. It remains an interesting challenge to elucidate how chemokine signaling mediated adhesion is coordinated with guidance to ensure correct migration. Moreover, it will be crucial to determine whether the integrin mediated adhesion mechanism operates in other examples of chemokine guidance such as migration of PGCs or the lateral line primordium.

Regulation of morphogenic migration

As we have seen, live imaging combined with genetic analyses has yielded a wealth of new information about how cell migration is regulated *in vivo*. A general theme that has emerged is that cell migration, in many cases is regulated at three different steps. Prior to migration, cells have a simple morphology and lack protrusions (Fig. 1A). In the first step, cells elaborate protrusions in all directions (Fig. 1B). In the second step, protrusions are oriented in the direction of migration and the cells move (Fig. 1C). Finally, in the third step cells cease moving upon reaching their destination (Fig. 1D). Although this concept was originally developed through the study of PGC migration (Blaser et al., 2005), it appears that it is generally applicable to most examples of embryonic cell migration. Below we highlight similarities as well as differences between the models discussed above (also see Table 1).

Acquisition of a complex cell morphology and protrusion formation

To begin migrating, a cell must gain competence to respond to directional cues and, in the case of cells of epithelial origin, detach from neighboring, non-motile cells (Fig. 1A). Although these processes are among the most clinically relevant aspects of morphogenic cell migration, they appear to be among the least well understood. In general, these processes involve downregulation of specific adhesion molecules involved in tissue integrity and upregulation or spatial segregation of components that regulate the cytoskeleton and generate dynamic traction forming adhesions. During this premigratory phase cells acquire a more complex morphology and begin to extend cell protrusions, such as thin fillipodia for guidance and larger lamellipodia for traction generation in a non-directed fashion.

One surprising conclusion from the study of developmental cell migration is that the molecular mechanisms that regulate the acquisition of motility are often distinct from the mechanisms that regulate later directional migration. For example, PGCs and lateral line primordium cells become motile in the absence of chemokine signaling molecules and border cells become motile in the absence of growth factor chemoattractants (Aman and Piotrowski, 2008; Haas and Gilmour, 2006; Valentin et al., 2007). Likewise, in zebrafish PGCs, overexpression of the chemokine guidance molecule *cxcl12a* does not lead to activation of intracellular chemokine signaling and directional cell migration until after PGCs have formed protrusions (Blaser et al., 2005). The onset of motility in gastrulation movements and neural crest migration also appear to be regulated by signaling pathways that are distinct from those necessary for guidance. The acquisition of protrusions in these cells is regulated by pathways that control EMT rather than guidance.

Table 1
Control of the three migratory stages in the different model organisms.

	I. Protrusion formation	II. Polarization and directional migration	III. Termination of migration
Vertebrate PGCs	Dead end: vertebrate-specific inhibitor of miRNAs	cxcr4b/7b-cxcl12	uniform cxcl12
Drosophila border cells	Cytokine-like ligand Unpaired Jak/Stat	Par1 Attractants: Gradient of PDGF-VEGF-like growth factor pv1 and grk, spi and krn. Receptors: pvi and egfr Jak/Stat for cohesiveness	uniform growth factors
Vertebrate lateral line	unknown	cxcr4b/7b-cxcl12 (likely no gradient)	uniform cxcl12?
Retina angiogenic sprouts	VEGF specifies tip cells	VEGF gradient	fusion with other vessels, relief of hypoxia leads to loss of VEGF expression
Vertebrate neural crest cells	EMT triggered by BMP, FGF and Wnt that activate snail and foxd3	repellants: robo/slit; neuropilin/semaphorin; ephrin/eph; Wnt/PCP attractants: cxcr4/cxcl12?	integration of repellant and attractive signals (e.g. ephrinB2 and N-cadherin)

These *in vivo* studies contradict conclusions drawn from *in vitro* studies, which put forward the attractive concept that chemoattractant gradients induce polarized cellular extensions on the side of the cell facing the higher concentration of chemoattractant (reviewed in Burridge and Wennerberg, 2004). Interestingly, independent regulation of protrusion acquisition and guided migration occurs in cells that migrate as isolated individuals, as well as cells migrating as multicellular collectives.

It is not known whether the regulation of protrusion formation is controlled by similar molecules across model systems. Regulation of this phase of migration is by far best understood in *Drosophila* border cells, where the coordinated activity of JAK/STAT, Notch and PCP signaling is necessary for the correct formation of protrusions (Bastock and Strutt, 2007; Beccari et al., 2002; Prasad and Montell, 2007). It remains to be investigated whether pathways uncovered in border cells also regulate this process in these other systems and therefore represent potentially conserved functional regulatory mechanisms. In PGCs, a micro-RNA binding molecule called 'Dead end' is necessary for the acquisition of motility but the down-stream mechanism is not understood (Weidinger et al., 2003). To date, no experimental manipulation has been able to abolish motile behavior from cells of the lateral line primordium.

In contrast to the model systems described above, acquisition of endothelial cell protrusions, as well as control of subsequent directional migration during formation of angiogenic sprouts in the mouse retina requires the same molecule, VEGF-A (Gerhardt et al., 2003). Therefore, while utilizing distinct regulatory mechanisms for the acquisition of motility and later directional migration may be a widespread phenomenon, it is not present in all migrating cells. Live imaging analysis of cell in which migration is blocked by loss of guidance information is necessary to evaluate whether a given cell fails to migrate due to failure to acquire protrusions or loss of guidance.

Polarization, detachment and directional migration

Once cells have gained the ability to generate protrusions and traction forces they become polarized and point their protrusions in the direction of migration. This process coincides with the onset of directional migration (Fig. 1B). Common to migrating cells is that they are guided via chemoattractant ligands, most commonly chemokines or growth factors, as in the examples discussed here. In neural crest cells repellant molecules also play an important role. The direction of migration is informed by gradients of these attractant and repellant molecules in the environment. Differences exist on how these gradients are generated and how the ensuing signals are interpreted intracellularly by the migrating cells leading to polarization of membrane protrusions and directional migration.

A chemoattractant gradient can be established via several mechanisms. The simplest mechanism to establish a chemoattractant gradient is free diffusion of ligand from the target tissue. For example in *Drosophila* border cell migration growth factor chemoattractants are produced in the oocyte from where they diffuse to the anterior pole of the egg chamber (McDonald et al., 2006; McDonald et al., 2003). A second mechanism involves the post-translational regulation of guidance ligands in extracellular space. A striking example is the formation of the Cxcl12 gradient via interactions with the newly described Cxcr7b receptor. Binding of Cxcl12a to Cxcr7b does not activate an intracellular signaling cascade, but rather leads to the internalization and destruction of Cxcl12a (Boldajipour et al., 2008). Thus, in PGCs, and likely in the lateral line primordium, Cxcr7b is involved in limiting the concentration of extracellular Cxcl12a chemoattractant in a spatially restricted manor. Therefore, loss of Cxcr7b leads to the failure of establishing a chemokine gradient and loss of directional migration.

Retinal vascular sprouts provide another example where post-translational regulation of guidance cues is important for correct gradient formation and directional migration. In this case the chemoattractant VEGF-A must associate with heparin present on neighboring astrocytes for efficient gradient formation (Gerhardt et al., 2003). Heparin likely plays a similar role in the regulation of gastrulation movements (Itoh and Sokol, 1994).

Similar mechanisms might be used to generate chemoattractant gradients as are employed in generating gradients of patterning morphogens. Recent studies of Fgf8 behavior suggest that free diffusion of signaling molecule coupled with receptor mediated endocytosis is sufficient to generate a stable gradient (Yu et al., 2009). Such a 'source-sink' model also operates in establishing Cxcl12a gradients that guide PGCs and the lateral line primordium toward their destinations, as described above.

Termination of migration

The final regulatory step of morphogenic cell movements is termination of migration when the cells reach their target sites (Fig. 1D). In general, this appears to be a relatively poorly understood aspect of cell migration. In cases where the molecular signals that stop migration have been elucidated, cells cease to migrate as they reach a region of locally high attractant or are surrounded by repulsive cues. For example, the highest concentration of growth factors is present close to the *Drosophila* oocyte in the egg chamber where border cells will contribute to the formation of the sperm entry site (McDonald et al., 2006; McDonald et al., 2003). Similarly, *cxcl12a* is highly expressed at the prospective gonad where zebrafish PGCs stop migrating (Doitsidou et al., 2002). In these cases, cells orient along a chemoattractant gradient and will not be able to leave a region of uniform or locally high guidance molecule concentration.

A second possible mechanism for the termination of migration could rely on physical impedance based on the morphology of the target tissue. For example, in the case of the posterior lateral line primordium and *Drosophila* border cells one might envision that the tail tip and the oocyte present physical barriers, respectively. In the egg chamber the oocyte is in direct contact with follicle cells on all sides. During migration, the border cell cluster is able to migrate between nurse cells, but once it reaches the oocyte, further migration would require cell invasion. However, in zebrafish PGCs the effect of a physical barrier and high levels of signaling can be dissociated. Aberrant chemokine signaling causes PGCs to overshoot past the gonads, and ectopic expression of *cxcl12a* can cause PGCs to stall in islands of highly *cxcl12a* expressing cells. These findings demonstrate that termination of PGC migration is not dependent on the presence of a physical barrier (Boldajipour et al., 2008; Reichman-Fried et al., 2004).

A third possibility is that other signaling interactions at these destinations lead to a loss of protrusions such that the cells are no longer able to respond to attractive cues altogether. As cells reach their target and differentiate, they could become non-motile and form functional components of mature organ systems. The *in vivo* factors that turn off motility have not been uncovered in any system but will likely involve the downregulation of factors that contribute to the initial acquisition of protrusions such as JAK/STAT signaling in border cells. This might make it difficult to evaluate this stopping mechanism in vivo, as loss of function in genes necessary for motility will result in impaired initiation of migration.

Finally, a fourth stopping mechanism is exemplified by angiogenic sprouts in the retina. As migrating sprouts reach their target locations they form new vessels permitting blood flow. Subsequently, the tissue is oxygenated, which relieves hypoxia. Hypoxia dependent VEGF-A expression is downregulated and the sprout tip loses protrusions (Gerhardt et al., 2003; Stone et al., 1995). Therefore, angiogenic sprouts trigger the downregulation of chemoattractant upon reaching their destination.

Resolution of these possibilities in a given system will require live imaging of clusters at the end of migration and conditional disruption

of gene function. If cells at the end of the migratory pathway are still motile, extend protrusions and tumble, a uniform level of attractant is likely causing cessation of migration. On the other hand, if cells lose motility altogether as they reach the target, it is more likely that other signals from the environment shut off cell motility. Elucidating such signals could have great clinical importance, as their inhibition might impede or prevent cancer dissemination by blocking the acquisition of motility. Although not as well studied as the other aspects of morphogenic collective migration, termination of migration is a vital step during morphogenesis with tremendous potential clinical interest that deserves more study in the future.

Additional considerations

Individual versus collective cell migration

A major difference between individually and collectively migrating cells is how they interact with their environment and how they sense/process directional cues. Although zebrafish PGCs and lateral line primordia rely on the same set of genes for guided migration, interesting differences between these systems spring from the fact that PGCs migrate as individual cells and the lateral line primordium migrates as a multicellular collective. During PGC migration Cxcr7b (a Cxcl12a sink) is dynamically expressed in non-migrating cells surrounding the migrating PGCs to sharpen a broad Cxcl12a gradient (Boldajipour et al., 2008). The lateral line primordium, however, expresses *cxcr7b* in migrating cells themselves enabling the primordium to migrate along a presumably uniform path of Cxcl12a (Aman and Piotrowski, 2008; Dambly-Chaudiere et al., 2007; Valentin et al., 2007). Thereby, directional information is created by signaling interaction within the migrating collective itself, as well as signals from the environment. Similarly, communication between cells in other migrating collectives such as border cells, neural crest cells and vascular sprouts are also vital for normal directional migration.

Another important difference is that collectively migrating cells modify the surrounding extracellular matrix (ECM), whereas individual cells squeeze through the ECM in an amoeboid fashion (Friedl and Gilmour, 2009; Friedl and Wolf, 2003). This finding by itself suggests that single cells should be able to migrate faster. However, in the systems thus far investigated, collective cell migration appears more efficient than single cell migration. For example isolated *Xenopus* mesodermal cells have difficulty migrating directionally along the blastocoel roof (Winklbauer et al., 1992). Also, neural crest cells in which cell–cell adhesion is compromised by disrupting N-cadherin migrate more slowly. Likewise, it has been reported that individual neural crest cells do not migrate well in vivo, likely because of a lack contact inhibition (Pla et al., 2001). One explanation for this phenomenon is that cells connected via cell–cell adhesion respond to forces coming from neighboring cells, whereas single cells solely rely on cell–substrate interactions. Also, groups of cells generate more force, as measured by the number of total focal adhesion points and traction forces (du Roure et al., 2005; Kolega et al., 1982). Another possible explanation for the efficiency of collective cell migration is that collectively migrating cells are more proficient in interpreting guidance signals. In general, a migrating collective spans more area than a single cell and can therefore potentially detect shallower gradients of guidance molecules. In addition, cell–cell communication in a migrating collective aids in directed migration. In collectively migrating cells only a few tip cells must perceive guidance cues (Haas and Gilmour, 2006), whereas individual cells continuously sample the environment to detect a gradient of an attractant. For example, individually migrating PGCs exhibit tumbling phases during which they do not move but explore the environment. The tumbling phase itself occurs cell-autonomously and independently of chemokine signaling and it was suggested that it might serve to redirect the cells (Reichman-Fried et al., 2004). Such tumbling phases are not observed in migrating collectives.

As single cell and collective cell migration occur simultaneously in an organism, the question arises whether cells are locked into their particular mode of migration. Surprisingly, studies of cancer cells revealed that migratory cells exhibit a large degree of plasticity. Collectively migrating cancer cells proteolytically degrade the extracellular matrix during forward migration. Disruption of their ability to remodel the surrounding ECM with pharmacological inhibitors of proteases was expected to yield groups of cells 'stuck' in the tissue. However, instead, these cancer cells switched their migratory mode from collective cell migration to a mesenchymal or amoeboid migration (Friedl and Wolf, 2003; Wolf et al., 2003).

An interesting question is whether collectively migrating cells during normal development are also able to migrate as individual cells if challenged. Manipulations of neural crest stream and border cell cluster integrity provide us with some answers. At a gross morphological level neural crest cells appear to migrate in loosely associated chains. However, scanning electron micrographs and live imaging have demonstrated that cells communicate via fillipodia and that cell–cell communication is crucial for directed migration (Bancroft and Bellairs, 1976; Davis and Trinkhaus, 1981; Teddy and Kulesa, 2004). For example, in transgenic mice with disrupted gap junction communication, cardiac neural crest cells migrate aberrantly (Sullivan et al., 1998). Gap junctions localized in cell membranes allow the passage of second messengers, ions and small metabolites, and thus could aid in transmitting guidance signals from leader cells to followers (Bruzzone et al., 1996).

A similar effect has been seen in *Drosophila* border cells in which the *hindsight* gene (*hnt*) is disrupted (Melani et al., 2008). *Hnt* is a negative regulator of JNK. JNK is essential for maintenance of cell polarity and cell–cell contacts. In its absence the border cell cluster disintegrates (Llense and MartÌn-Blanco, 2008). Nevertheless, individual border cells still migrate slowly, as long as they maintain contact with the polar cells while extending multiple protrusions in all directions. Thus, motility of groups of cells, such as neural crest and border cells does not absolutely depend on cohesiveness of the migrating cells, however, when isolated, these cells fail to undergo proper morphogenesis. It has not been determined yet if this failure is caused by an inability to efficiently integrate guidance cues, or whether their slowed migration causes them to reach their targets too late, at which point signals from the environment have changed. Likely, as cancer cells do not follow a precise developmental program and form morphological structures that have to be integrated into the organ system, they are more flexible with respect to their migration mode. During development however, changes in the mode of migration appear detrimental for morphogenesis.

Epithelial polarity and migration

Neural crest and many cancer cells undergo an EMT as they begin to migrate (Thiery, 2003). For these cell types it is essential to lose their polarity, so they can emigrate from the neural tube or away from a tumor. However, border cells remain apico-basally polarized during migration with their apical domains facing away from the polar cells. This configuration is established by the action of the Par/aPKC polarity complex (McDonald et al., 2008). Lateral line primordium cells are also apico-basally polarized while migrating, which also requires the action of classical apico-basal determinants such as aPKC. aPKC localizes zonula adherens junctions to the distal side of cells (the side facing away from the somites) likely by regulating the localization of Par proteins (Hava et al., 2009). In the trailing two-thirds of the primordium apico-basally polarized cells constrict apically leading to the formation of rosette shaped proneuromasts (Lecaudey et al., 2008). In addition, sensory hair cells in deposited neuromasts are also polarized with cilia either oriented in parallel or perpendicular to the

antero-posterior axis (Lopez-Schier and Hudspeth, 2006). However, it has not yet been determined whether hair cell polarity is established in the precursors during migration or only once proneuromasts are deposited.

Even though apical–basal cell polarity is essential for the initiation of border cell migration, it is likely not required for lateral line primordium migration as has been previously suggested (Lecaudey et al., 2008). Inactivation of Wnt/β-catenin signaling in the cluster leads to the loss of Fgf signaling (Aman and Piotrowski, 2008). Loss of Fgf signaling, in turn, is accompanied by a loss of apico-basal polarity and rosette formation (Lecaudey et al., 2008; Nechiporuk and Raible, 2008). Yet, in the absence of Wnt/β-catenin signaling primordia still migrate to the tip of the tail, even though they fail to form and deposit proneuromasts (Aman and Piotrowski, 2008).

In contrast to apico-basal polarity, polarity of cellular protrusions is indispensable for directed migration. All migrating cells elaborate cellular extensions that presumably help generate the traction forces necessary for directional migration. As mentioned above, protrusion polarity is controlled by gradients of chemoattractant signaling molecules. For example, in the absence of Cxcl12a, PGCs and lateral line primordium cells form protrusions in random positions, cells begin to tumble and migration stalls. Thus, chemoattractant induced cell polarity is essential for directed cell migration in all well studied model systems, whereas apico-basal polarity is only required in a few.

Induction of motility as a mechanism to activate dormant cancer stem cells?

Jak/Stat signaling has been recognized as an important target in cancer therapy, as Jak/Stat signaling is essential for the onset of migration, directed cell migration and homing of many cancer cell types to particular organs where they form metastases (Liang et al., 2004). Signals that activate Jak/Stat signaling during these migratory events are, for example, chemokines and cytokines, such as Cxcl12 and interferons (Essers et al., 2009; Vila-Coro et al., 1999). Inhibiting the onset of migration is a powerful approach to inhibit cancer cell dissemination. However, in other instances, such as leukemia stem cells, it might be advantageous to promote cell motility. Dormant leukemia stem cells divide very rarely and are therefore not susceptible to antiproliferative drugs (Essers et al., 2009; Goldman and Gordon, 2006; Lerner, 1990). The persistence of dormant stem cells in the bone marrow causes a high remission rate among cancer patients after treatment. Recent elegant work by Essers et al. (2009) has shown that dormant hematopoietic stem cells (HSCs) can be activated by interferon alpha (INFα), a cytokine produced during an inflammatory response or during infections. Treated, activated HSCs begin to proliferate and are efficiently targeted and depleted by chemotherapeutic agents. INFα mediates its effects via Jak/Stat signaling and it is thought that activation of JAK/STAT leads to proliferation of stem cells (Briscoe et al., 1996; Darnell et al., 1994; Essers et al., 2009; van Boxel-Dezaire et al., 2006). However, as onset of proliferation normally coincides with stem cells leaving their niche (Wilson and Trumpp, 2006), an attractive hypothesis is that activation of JAK/STAT primarily causes the onset of motility of dormant stem cells. As described above, chemokines also signal via JAK/STAT (Vila-Coro et al., 1999). Chemokine signaling has been shown to be essential for homing and mobilization of neutrophils. In the presence of high levels of the chemokine ligand CXCL12 neutrophils leave their niche in the bone marrow (Furze and Rankin, 2008). These observations raise the possibility that IFNα might activate/mobilize stem cells via the induction of chemokine receptors. This hypothesis is conceivable as IFNα upregulates *cxcr4* in HSCs *in vitro* (Tabe et al., 2007). Alternatively, IFNα and chemokines could converge on the JAK/STAT pathway and thus function in a cooperative manner. Clearly, it would be very interesting to determine the downstream targets and resulting cell behaviors of JAK/STAT signaling in stem cell activation, as this knowledge would provide us with additional targets.

Concluding remarks

Although cell migration is a complex process, live imaging and genetic approaches are yielding much information and will continue to do so. Understanding these processes in genetically tractable model systems will allow deeper understanding of the origin of form and how these mechanisms contribute to human disease. Morphogenic cell migration is a highly dynamic process that can be regulated at the level of acquisition of motility, guidance of directional migration and termination of migration. Experimental interference with any of these processes can lead to aberrant migration and resulting defects in morphogenesis. Live imaging is therefore preferred to examine the precise cellular defects causing such phenotypes. For instance, loss of guidance information can closely resemble loss of motility at a gross phenotypic level. High resolution imaging of cells in fixed samples might reveal the presence of an elaborate cell morphology associated with motility but such processes can be small and short lived and difficult to observe as is the case for *Drosophila* border cells (Prasad and Montell, 2007).

Especially interesting questions that we will have to answer are how adhesion molecules contribute to morphogenic processes. Recent work by Nair and Schilling has demonstrated that chemokines regulate integrin–fibronectin mediated adhesion in migrating endoderm (Nair and Schilling, 2008). These findings raise the possibility that adhesion and guidance might be mechanistically linked in other examples of chemokine mediated migration as well. Additionally, several studies have shown that adhesion molecules not only influence migration via cell–cell adhesion but also via directly regulating the cytoskeleton and protrusion formation.

Also, it is not fully understood how cells migrating in tightly adhering clusters of cells, such as the lateral line primordium, communicate with each other to coordinate their directional migration. Chemokine signaling is required in leading cells but not in trailing cells in the center of the lateral line primordium. As these cells also tumble in the absence of chemokine signaling, they are either mechanically influenced by leading cells or receive, as yet unidentified chemical signals.

Finally, cell migration must be coordinated with other basic cell behaviors such as cell growth, proliferation and shape changes. How these cell behaviors are orchestrated to produce complex three dimensional morphologies remains among the greatest challenges facing modern biology. As misregulation of migration can cause disease, an appreciation of the molecules involved in morphogenic cell migration may also lead to novel therapeutic avenues aimed at the treatment and prevention of cancer invasion and metastasis.

References

Acloque, H., 2009. Epithelial–mesenchymal transitions: the importance of changing cell state in development and disease. J. Clin. Invest. 119, 1438–1449.
Aman, A., Piotrowski, T., 2008. Wnt/β-catenin and Fgf signaling control collective cell migration by restricting chemokine receptor expression. Dev. Cell 15, 749–761.
Aman, A., piotrowski, T., 2009. Multiple signaling interactions coordinate collective cell migration of the posterior lateral line primordium. Cell Adhes. Migration 3 electronic publication ahead of print.
Bancroft, M., Bellairs, R., 1976. The development of the notochord in the chick embryo, studied by scanning and transmission electron microscopy. J. Embryol. Exp. Morphol. 35, 383–401.
Bastock, R., Strutt, D., 2007. The planar polarity pathway promotes coordinated cell migration during Drosophila oogenesis. Development 134, 3055–3064.
Beccari, S., Teixeira, L., Rorth, P., 2002. The JAK/STAT pathway is required for border cell migration during Drosophila oogenesis. Mech. Dev. 111, 115–123.
Belmadani, A., Tran, P.B., Ren, D., Assimacopoulos, S., Grove, E.A., Miller, R.J., 2005. The chemokine stromal cell-derived factor-1 regulates the migration of sensory neuron progenitors. J. Neurosci. 25, 3995–4003.
Benini, S., Perbal, B., Zambelli, D., Colombo, M.P., Manara, M.C., Serra, M., Parenza, M., Martinez, V., Picci, P., Scotlandi, K., 2005. In Ewing's sarcoma CCN3(NOV) inhibits

proliferation while promoting migration and invasion of the same cell type. Oncogene 24, 4349–4361.
Bianco, A., Poukkula, M., Cliffe, A., Mathieu, J., Luque, C.M., Fulga, T.A., Rorth, P., 2007. Two distinct modes of guidance signalling during collective migration of border cells. Nature 448, 362–365.
Blaser, H., Eisenbeiss, S., Neumann, M., Reichman-Fried, M., Thisse, B., Thisse, C., Raz, E., 2005. Transition from non-motile behaviour to directed migration during early PGC development in zebrafish. J. Cell. Sci. 118, 4027–4038.
Blaser, H., Reichman-Fried, M., Castanon, I., Dumstrei, K., Marlow, Florence, L., Kawakami, K., Solnica-Krezel, L., Heisenberg, C.P., Raz, E., 2006. Migration of zebrafish primordial germ cells: a role for myosin contraction and cytoplasmic flow. Dev. Cell 11, 613–627.
Boldajipour, B., Mahabaleshwar, H., Kardash, E., Reichman-Fried, M., Blaser, H., Minina, S., Wilson, D., Xu, Q., Raz, E., 2008. Control of chemokine-guided cell migration by ligand sequestration. Cell 132, 463–473.
Briscoe, J., Guschin, D., Rogers, N.C., Watling, D., Muller, M., Horn, F., Heinrich, P., Stark, G.R., Kerr, I.M., Karin, M., Parker, P.J., Marshall, C.J., Ihle, J.N., 1996. JAKs, STATs and signal transduction in response to the interferons and other cytokines [and discussion]. Philos. Trans. R. Soc. London. Ser. B: Biol. Sci. 351, 167–171.
Burridge, K., Wennerberg, K., 2004. Rho and Rac take center stage. Cell 116, 167–179.
Carmona-Fontaine, C., Matthews, H.K., Kuriyama, S., Moreno, M., Dunn, G.A., Parsons, M., Stern, C.D., Mayor, R., 2008. Contact inhibition of locomotion in vivo controls neural crest directional migration. Nature 456, 957–961.
Carver, E.A., Jiang, R., Lan, Y., Oram, K.F., Gridley, T., 2001. The mouse snail gene encodes a key regulator of the epithelial–mesenchymal transition. Mol. Cell Biol. 21, 8184–8188.
Chen, X., Macara, I.G., 2005. Par-3 controls tight junction assembly through the Rac exchange factor Tiam1. Nat. Cell Biol. 7, 262–269.
Ciruna, B., Rossant, J., 2001. FGF signaling regulates mesoderm cell fate specification and morphogenetic movement at the primitive streak. Dev. Cell. 1, 37–49.
Claxton, S., Fruttiger, M., 2004. Periodic Delta-like 4 expression in developing retinal arteries. Gene Expr. Patterns 5, 123–127.
Cvejic, A., Hall, C., Bak-Maier, M., Flores, M.V., Crosier, P., Redd, M.J., Martin, P., 2008. Analysis of WASp function during the wound inflammatory response—live-imaging studies in zebrafish larvae. J. Cell. Sci. 121, 3196–3206.
Dambly-Chaudiere, C., Cubedo, N., Ghysen, A., 2007. Control of cell migration in the development of the posterior lateral line: antagonistic interactions between the chemokine receptors CXCR4 and CXCR7/RDC1. BMC Dev. Biol. 7, 23.
Darnell Jr, J.E., Kerr, I.M., Stark, G.R., 1994. Jak–STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science 264, 1415–1421.
David, N.B., Sapede, D., Saint-Etienne, L., Thisse, C., Thisse, B., Dambly-Chaudiere, C., Rosa, F.M., Ghysen, A., 2002. Molecular basis of cell migration in the fish lateral line: Role of the chemokine receptor CXCR4 and of its ligand, SDF1. Proc. Natl. Acad. Sci. U. S. A. 99, 16297–16302.
Davidson, L.A., Hoffstrom, B.G., Keller, R., DeSimone, D.W., 2002. Mesendoderm extension and mantle closure in Xenopus laevis gastrulation: combined roles for integrin [alpha]5[beta]1, fibronectin, and tissue geometry. Dev. Biol. 242, 109–129.
Davidson, L.A., Marsden, M., Keller, R., DeSimone, D.W., 2006. Integrinalpha(5)beta(1) and fibronectin regulate polarized cell protrusions required for Xenopus convergence and extension. Curr. Biol. 16, 833–844.
Davis, E.M., Trinkhaus, J.P., 1981. Significance of cell-to-cell contacts for the directional movement of neural crest cells within a hydrated collagen lattice. J. Embryol. Exp. Morphol. 63, 29–51.
De Calisto, J., Araya, C., Marchant, L., Riaz, C.F., Mayor, R., 2005. Essential role of non-canonical Wnt signalling in neural crest migration. Development 132, 2587–2597.
De Smet, F., Segura, I., De Bock, K., Hohensinner, P.J., Carmeliet, P., 2009. Mechanisms of vessel branching: filopodia on endothelial tip cells lead the way. Arterioscler. Thromb. Vasc. Biol. 29, 639–649.
Doitsidou, M., Reichman-Fried, M., Stebler, J., Koprunner, M., Dorries, J., Meyer, D., Esguerra, C.V., Leung, T., Raz, E., 2002. Guidance of primordial germ cell migration by the chemokine SDF-1. Cell 111, 647–659.
Duchek, P., Somogyi, K., Jekely, G., Beccari, S., Rorth, P., 2001. Guidance of cell migration by the Drosophila PDGF/VEGF receptor. Cell 107, 17–26.
du Roure, O., Saez, A., Buguin, A., Austin, R.H., Chavrier, P., Siberzan, P., Ladoux, B., 2005. Force mapping in epithelial cell migration. Proc. Natl. Acad. Sci. U. S. A. 102, 2390–2395.
Essers, M.A.G., Offner, S., Blanco-Bose, W.E., Waibler, Z., Kalinke, U., Duchosal, M.A., Trumpp, A., 2009. IFN[agr] activates dormant haematopoietic stem cells in vivo. Nature 458, 904–908.
Friedl, P., Gilmour, D., 2009. Collective cell migration in morphogenesis, regeneration and cancer. Nat. Rev. Mol. Cell Biol. 10, 445–457.
Friedl, P., Wolf, K., 2003. Tumour-cell invasion and migration: diversity and escape mechanisms. Nat. Rev. Cancer 3, 362–374.
Friedl, P., Borgmann, S., Brocker, E.B., 2001. Amoeboid leukocyte crawling through extracellular matrix: lessons from the Dictyostelium paradigm of cell movement. J. Leukoc. Biol. 70, 491–509.
Fruttiger, M., 2007. Development of the retinal vasculature. Angiogenesis 10, 77–88.
Fukui, A., Goto, T., Kitamoto, J., Homma, M., Asashima, M., 2007. SDF-1[alpha] regulates mesendodermal cell migration during frog gastrulation. Biochem. Biophys. Res. Commun. 354, 472–477.
Furze, R.C., Rankin, S.M., 2008. The role of the bone marrow in neutrophil clearance under homeostatic conditions in the mouse. FASEB J. 22, 3111–3119.
Gerhardt, H., 2008. VEGF and endothelial guidance in angiogenic sprouting. Organogenesis 4, 241–246.
Gerhardt, H., Golding, M., Fruttiger, M., Ruhrberg, C., Lundkvist, A., Abramsson, A., Jeltsch, M., Mitchell, C., Alitalo, K., Shima, D., Betsholtz, C., 2003. VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. J. Cell Biol. 161, 1163–1177.
Ghiglione, C., Devergne, O., Georgenthum, E., Carballes, F., Medioni, C., Cerezo, D., Noselli, S., 2002. The Drosophila cytokine receptor Domeless controls border cell migration and epithelial polarization during oogenesis. Development 129, 5437–5447.
Ghysen, A., Dambly-Chaudiere, C., 2004. Development of the zebrafish lateral line. Curr. Opin. Neurobiol. 14, 67–73.
Goldman, J., Gordon, M., 2006. Why do chronic myelogenous leukemia stem cells survive allogeneic stem cell transplantation or imatinib: does it really matter? Leuk. Lymph. 47, 1–7.
Haas, P., Gilmour, D., 2006. Chemokine signaling mediates self-organizing tissue migration in the zebrafish lateral line. Dev. Cell 10, 673–680.
Hammerschmidt, M., Wedlich, D., 2008. Regulated adhesion as a driving force of gastrulation movements. Development 135, 3625–3641.
Hava, D., Forster, U., Matsuda, M., Cui, S., Link, B.A., Eichhorst, J., Wiesner, B., Chitnis, A., Abdelilah-Seyfried, S., 2009. Apical membrane maturation and cellular rosette formation during morphogenesis of the zebrafish lateral line. J. Cell. Sci. 122, 687–695.
Hellström, M., Phng, L.K., Hofmann, J.J., Wallgard, E., Coultas, L., Lindblom, P., Alva, J., Nilsson, A.K., Karlsson, L., Gaiano, N., Yoon, K., Rossant, J., Iruela-Arispe, M.L., Kalén, M., Gerhardt, H., Betsholtz, C., 2007. Dll4 signalling through Notch1 regulates formation of tip cells during angiogenesis. Nature 445, 776–780.
Hirose, T., Izumi, Y., Nagashima, Y., Tamai-Nagai, Y., Kurihara, H., Sakai, T., Suzuki, Y., Yamanaka, T., Suzuki, A., Mizuno, K., Ohno, S., 2002. Involvement of ASIP/PAR-3 in the promotion of epithelial tight junction formation. J. Cell. Sci. 115, 2485–2495.
Ikenouchi, J., Matsuda, M., Furuse, M., Tsukita, S., 2003. Regulation of tight junctions during the epithelium–mesenchyme transition: direct repression of the gene expression of claudins/occludin by Snail. J. Cell. Sci. 116, 1959–1967.
Itoh, K., Sokol, S., 1994. Heparan sulfate proteoglycans are required for mesoderm formation in Xenopus embryos. Development 120, 2703–2711.
Jaffe, A.B., Hall, A., 2005. RHO GTPASES: biochemistry and biology. Ann. Rev. Cell Dev. Biol. 21, 247.
Jekely, G.S., Hsin-Ho, Luque, C.M., Rorth, P., 2005. Regulators of endocytosis maintain localized receptor tyrosine kinase signaling in guided migration. Dev. Cell 9, 197–207.
Kane, D.A., McFarland, K.N., Warga, R.M., 2005. Mutations in half baked/E-cadherin block cell behaviors that are necessary for teleost epiboly. Development 132, 1105–1116.
Kasemeier-Kulesa, J.C., Bradley, R., Pasquale, E.B., Lefcort, F., Kulesa, P.M., 2006. Eph/ephrins and N-cadherin coordinate to control the pattern of sympathetic ganglia. Development 133, 4839–4847.
Kashef, J., Kohler, A., Kuriyama, S., Alfandari, D., Mayor, R., Wedlich, D., 2009. Cadherin-11 regulates protrusive activity in Xenopus cranial neural crest cells upstream of Trio and the small GTPases. Genes Dev. 23, 1393–1398.
Kedde, M., Strasser, M.J., Boldajipour, B., Oude Vrielink, J.A., Slanchev, K., le Sage, C., Nagel, R., Voorhoeve, P.M., van Duijse, J., Orom, U.A., Lund, A.H., Perrakis, A., Raz, E., Agami, R., 2007. RNA-binding protein Dnd1 inhibits microRNA access to target mRNA. Cell 131, 1273–1286.
Keller, R., 2005. Cell migration during gastrulation. Curr. Opin. Cell Biol. 17, 533–541.
Kerstetter, A.E., Azodi, A., Liu, Q., 2004. Cadherin-2 function in the cranial ganglia and lateral line system of developing zebrafish. Dev. Dyn. 230, 137–143.
Knaut, H., Werz, C., Geisler, R., The Tubingen Screen, C., Nusslein-Volhard, C., 2003. A zebrafish homologue of the chemokine receptor Cxcr4 is a germ-cell guidance receptor. Nature 421, 279–282.
Knecht, A.K., Bronner-Fraser, M., 2002. Induction of the neural crest: a multigene process. Nat. Rev. Genet. 3, 453–461.
Kolega, J.S.M., Chen, W.T., Young, N.D., 1982. Rapid cellular translocation is related to close contacts formed between various cultured cells and their substrata. J. Cell. Sci. 54, 23–34.
Kozlowski, D.J., Murakami, T., Ho, R.K., Weinberg, E.S., 1997. Regional cell movement and tissue patterning in the zebrafish embryo revealed by fate mapping with caged fluorescein. Biochem. Cell. Biol. 75, 551–562.
Krebs, L.T., Xue, Y., Norton, C.R., Shutter, J.R., Maguire, M., Sundberg, J.P., Gallahan, D., Closson, V., Kitajewski, J., Callahan, R., Smith, G.H., Stark, K.L., Gridley, T., 2000. Notch signaling is essential for vascular morphogenesis in mice. Genes Dev. 14, 1343–1352.
Kunwar, P.S., Siekhaus, D.E., Lehmann, R., 2006. In vivo migration: a germ cell perspective. Annu. Rev. Cell Dev. Biol. 22, 237.
Kuriyama, S., Mayor, R., 2008. Molecular analysis of neural crest migration. Philos. Trans. R. Soc. B:. Biol. Sci. 363, 1349–1362.
Lawson, A., Schoenwolf, G.C., 2001. Cell populations and morphogenetic movements underlying formation of the avian primitive streak and organizer. Genesis 29, 188–195.
Lecaudey, V., Cakan-Akdogan, G., Norton, W.H.J., Gilmour, D., 2008. Dynamic Fgf signaling couples morphogenesis and migration in the zebrafish lateral line primordium. Development 135, 2695–2705.
Le Douarin, N.M., 2004. The avian embryo as a model to study the development of the neural crest: a long and still ongoing story. Mech. Dev. 121, 1089–1102.
Lerner, C.H.D., 1990. 5-Fluorouracil spares hemopoietic stem cells responsible for long-term repopulation. Exp. Hematol. 18, 114–118.
Li, K., Kuwada, J.Y., 2004. Chemokine signaling regulates sensory cell migration in zebrafish. Dev. Biol. 269, 123–136.
Liang, Z., Wu, T., Lou, H., Yu, X., Taichman, R.S., Lau, S.K., Nie, S., Umbreit, J., Shim, H., 2004. Inhibition of breast cancer metastasis by selective synthetic polypeptide against CXCR4. Cancer Res. 64, 4302–4308.

Llense, F., MartÌn-Blanco, E., 2008. JNK signaling controls border cell cluster integrity and collective cell migration. Curr. Biol. 18, 538–544.
Lopez-Schier, H., Hudspeth, A.J., 2006. A two-step mechanism underlies the planar polarization of regenerating sensory hair cells. Proc. Natl. Acad. Sci. 103, 18615–18620.
Marsden, M., DeSimone, D.W., 2001. Regulation of cell polarity, radial intercalation and epiboly in Xenopus: novel roles for integrin and fibronectin. Development 128, 3635–3647.
McDonald, J.A., Pinheiro, E.M., Montell, D.J., 2003. PVF1, a PDGF/VEGF homolog, is sufficient to guide border cells and interacts genetically with Taiman. Development 130, 3469–3478.
McDonald, J.A., Pinheiro, E.M., Kadlec, L., Schupbach, T., Montell, D.J., 2006. Multiple EGFR ligands participate in guiding migrating border cells. Dev. Biol. 296, 94–103.
McDonald, J.A., Khodyakova, A., Aranjuez, G., Dudley, C., Montell, D.J., 2008. PAR-1 kinase regulates epithelial detachment and directional protrusion of migrating border cells. Curr. Biol. 18, 1659–1667.
Melani, M., Simpson, K.J., Brugge, J.S., Montell, D., 2008. Regulation of cell adhesion and collective cell migration by hindsight and its human homolog RREB1. Curr. Biol. 18, 532–537.
Metcalfe, W.K., Kimmel, C.B., Schabtach, E., 1985. Anatomy of the posterior lateral line system in young larvae of the zebrafish. J. Comp. Neurol. 233, 377–389.
Mizoguchi, T., Verkade, H., Heath, J.K., Kuroiwa, A., Kikuchi, Y., 2008. Sdf1/Cxcr4 signaling controls the dorsal migration of endodermal cells during zebrafish gastrulation. Development 135, 2521–2529.
Molyneaux, K.A., Zinszner, H., Kunwar, P.S., Schaible, K., Stebler, J., Sunshine, M.J., O'Brien, W., Raz, E., Littman, D., Wylie, C., Lehmann, R., 2003. The chemokine SDF1/CXCL12 and its receptor CXCR4 regulate mouse germ cell migration and survival. Development 130, 4279–4286.
Montell, D.J., 2001. Command and control: regulatory pathways controlling invasive behavior of the border cells. Mech. Dev. 105, 19–25.
Montell, D.J., 2003. Border-cell migration: the race is on. Nat. Rev. Mol. Cell Biol. 4, 13–24.
Montell, D.J., Rorth, P., Spradling, A.C., 1992. Slow border cells, a locus required for a developmentally regulated cell migration during oogenesis, encodes Drosophila C/EBP. Cell 71, 51–62.
Montero, J.A., Carvalho, L., Wilsch-Brauninger, M., Kilian, B., Mustafa, C., Heisenberg, C.P., 2005. Shield formation at the onset of zebrafish gastrulation. Development 132, 1187–1198.
Nagel, M., Tahinci, E., Symes, K., Winklbauer, R., 2004. Guidance of mesoderm cell migration in the Xenopus gastrula requires PDGF signaling. Development 131, 2727–2736.
Nair, S., Schilling, T.F., 2008. Chemokine signaling controls endodermal migration during zebrafish gastrulation. Science 322, 89–92.
Nechiporuk, A., Raible, D.W., 2008. FGF-dependent mechanosensory organ patterning in zebrafish. Science 320, 1774–1777.
Nieto, M.A., 2002. The snail superfamily of zinc-finger transcription factors. Nat. Rev. Mol. Cell Biol. 3, 155–166.
Pla, P., Moore, R., Morali, O.G., Grille, S., Martinozzi, S., Delmas, V., Larue, L., 2001. Cadherins in neural crest cell development and transformation. J. Cell. Physiol. 189, 121–132.
Peinado, H., Olmeda, D., Cano, A., 2007. Snail, Zeb and bHLH factors in tumour progression: an alliance against the epithelial phenotype. Nat. Rev. Cancer 7, 415–428.
Pézeron, G., Mourrain, P., Courty, S., Ghislain, J., Becker, T.S., Rosa, F.M., David, N.B., 2008. Live analysis of endodermal layer formation identifies random walk as a novel gastrulation movement. Curr. Biol. 18, 276–281.
Piotrowski, T., Northcutt, R.G., 1996. The cranial nerves of the Senegal bichir, Polypterus senegalus [osteichthyes: actinopterygii: cladistia]. Brain Behav. Evol. 47, 55–102.
Prasad, M., Montell, D.J., 2007. Cellular and molecular mechanisms of border cell migration analyzed using time-lapse live-cell imaging. Dev. Cell 12, 997–1005.
Raz, E., 2003. Primordial germ-cell development: the zebrafish perspective. Nat. Rev. Genet. 4, 690–700.
Raz, E., Reichman-Fried, M., 2006. Attraction rules: germ cell migration in zebrafish. Curr. Opin. Genet. Dev. 16, 355–359.
Reichman-Fried, M., Minina, S., Raz, E., 2004. Autonomous modes of behavior in primordial germ cell migration. Dev. Cell 6, 589–596.
Ren, R., Nagel, M., Tahinci, E., Winklbauer, R., Symes, K., 2006. Migrating anterior mesoderm cells and intercalating trunk mesoderm cells have distinct responses to Rho and Rac during Xenopus gastrulation. Dev. Dyn. 235, 1090–1099.
Bruzzone, R., White, T.W., Paul, D.L., 1996. Connections with connexins: the molecular basis of direct intercellular signaling. Eur. J. Biochem. 238, 1–27.
Rohde, L.A., Heisenberg, C.P., 2007. Zebrafish gastrulation: cell movements, signals, and mechanisms. Int. Rev. Cytol. 261, 159–192.
Rorth, P., 2002. Initiating and guiding migration: lessons from border cells. Trends Cell Biol. 12, 325–331.
Rorth, P., 2007. Collective guidance of collective cell migration. Trends Cell Biol. 17, 575–579.
Rupp, P.A., Kulesa, P.M., 2007. A role for RhoA in the two-phase migratory pattern of post-otic neural crest cells. Dev. Biol. 311, 159–171.
Sapede, D., Gompel, N., Dambly-Chaudiere, C., Ghysen, A., 2002. Cell migration in the postembryonic development of the fish lateral line. Development 129, 605–615.
Schlosser, G., 2006. Induction and specification of cranial placodes. Dev. Biol. 294, 303–351.
Schlosser, G., Northcutt, R.G., 2000. Development of neurogenic placodes in <I>Xenopus laevis</I>. J. Comp. Neurol. 418, 121–146.
Silver, D.L., Montell, D.J., 2001. Paracrine signaling through the JAK/STAT pathway activates invasive behavior of ovarian epithelial cells in Drosophila. Dev. Cell 107, 831–841.
Silver, D.L., Geisbrecht, E.R., Montell, D.J., 2005. Requirement for JAK/STAT signaling throughout border cell migration in Drosophila. Development 132, 3483–3492.
Solnica-Krezel, L., 2005. Conserved patterns of cell movements during vertebrate gastrulation. Curr. Biol. 15, 213–228.
Solnica-Krezel, L., 2006. Gastrulation in zebrafish—all just about adhesion? Curr. Opin. Genet. Dev. 16, 433–441.
Stebler, J.r., Spieler, D., Slanchev, K., Molyneaux, K.A., Richter, U., Cojocaru, V., Tarabykin, V., Wylie, C., Kessel, M., Raz, E., 2004. Primordial germ cell migration in the chick and mouse embryo: the role of the chemokine SDF-1/CXCL12. Dev. Biol. 272, 351–361.
Stone, J., Itin, A., Alon, T., Pe'er, J., Gnessin, H., Chan-Ling, T., Keshet, E., 1995. Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. J. Neurosci. 15, 4738–4747.
Sullivan, R., Huang, G.Y., Meyer, R.A., Wessels, A., Linask, K.K., Lo, C.W., 1998. Heart malformations in transgenic mice exhibiting dominant negative inhibition of gap junctional communication in neural crest cells. Dev. Biol. 204, 224–234.
Tabe, Y., Jin, L., Tsutsumi-Ishii, Y., Xu, Y., McQueen, T., Priebe, W., Mills, G.B., Ohsaka, A., Nagaoka, I., Andreeff, M., Konopleva, M., 2007. Activation of integrin-linked kinase is a critical prosurvival pathway induced in leukemic cells by bone marrow-derived stromal cells. Cancer Res. 67, 684–694.
Taneyhill, L.A., 2008. To adhere or not to adhere: The role of Cadherins in neural crest development. Cell Adh. Migr. 2, 223–230.
Teddy, J.M., Kulesa, P.M., 2004. In vivo evidence for short- and long-range cell communication in cranial neural crest cells. Development 131, 6141–6151.
Thiery, J.P., 2003. Epithelial–mesenchymal transitions in development and pathologies. Curr. Opin. Cell Biol. 15, 740–746.
Thisse, B., Pflumio, S., Fürthauer, M., Loppin, B., Heyer, V., Degrave, A., Woehl, R., Lux, A., Steffan, T., Charbonnier, X.Q. and Thisse, C., 2001. ZFIN Direct Data Submission (http://zfin.org).
Uemura, A., Kusuhara, S., Katsuta, H., Nishikawa, S.I., 2006. Angiogenesis in the mouse retina: a model system for experimental manipulation. Exp. Cell Res. 312, 676–683.
Ulrich, F., Concha, M.L., Heid, P.J., Voss, E., Witzel, S., Roehl, H., Tada, M., Wilson, S.W., Adams, R.J., Soll, D.R., Heisenberg, C.P., 2003. Slb/Wnt11 controls hypoblast cell migration and morphogenesis at the onset of zebrafish gastrulation. Development 130, 5375–5384.
Valentin, G., Haas, P., Gilmour, D., 2007. The chemokine SDF1a coordinates tissue migration through the spatially restricted activation of Cxcr7 and Cxcr4b. Curr. Biol. 17, 1026–1031.
van Boxel-Dezaire, A.H.H., Rani, M.R.S., Stark, G.R., 2006. Complex modulation of cell type-specific signaling in response to type I interferons. Immunity 25, 361–372.
Vasilyev, A., Liu, Y., Mudumana, S., Mangos, S., Lam, P.Y., Majumdar, A., Zhao, J., Poon, K. L., Kondrychyn, I., Korzh, V., Drummond, I.A., 2009. Collective cell migration drives morphogenesis of the kidney nephron. PLoS Biol. 7, e1000009.
Vila-Coro, A.J., Rodriquez-Frade, J.M., Martin De Ana, A., Moreno-Ortiz, M.C., Martinez, C., Mellado, M., 1999. The chemokine SDF-1{alpha} triggers CXCR4 receptor dimerization and activates the JAK/STAT pathway. FASEB J. 13, 1699–1710.
Wang, X., Bo, J., Bridges, T., Dugan, K.D., Pan, T.c., Chodosh, L.A., Montell, D.J., 2006. Analysis of cell migration using whole-genome expression profiling of migratory cells in the Drosophila ovary. Dev. Cell 10, 483–495.
Weidinger, G., Stebler, J.r., Slanchev, K., Dumstrei, K., Wise, C., Lovell-Badge, R., Thisse, C., Thisse, B., Raz, E., 2003. Dead end, a novel vertebrate germ plasm component, is required for zebrafish primordial germ cell migration and survival. Curr. Biol. 13, 1429–1434.
Wilson, A., Trumpp, A., 2006. Bone-marrow haematopoietic-stem-cell niches. Nat. Rev. Immunol. 6, 93–106.
Winklbauer, R., Keller, R.E., 1996. Fibronectin, mesoderm migration, and gastrulation in Xenopus. Dev. Biol. 177, 413–426.
Winklbauer, R., Nagel, M., 1991. Directional mesoderm cell migration in the Xenopus gastrula. Dev. Biol. 148, 573–589.
Winklbauer, R., Selchow, A., 1992. Motile behavior and protrusive activity of migratory mesoderm cells from the Xenopus gastrula. Dev. Biol. 150, 335–351.
Winklbauer, R., Selchow, A., Nagel, M., Angres, B., 1992. Cell interaction and its role in mesoderm cell migration during Xenopus gastrulation. Dev. Dyn. 195, 290–302.
Winklbauer, R., Nagel, M., Selchow, A., Wacker, S., 1996. Mesoderm migration in the Xenopus gastrula. Int. J. Dev. Biol. 40, 305–311.
Witzel, S., Zimyanin, V., Carreira-Barbosa, F., Tada, M., Heisenberg, C.P., 2006. Wnt11 controls cell contact persistence by local accumulation of Frizzled 7 at the plasma membrane. J. Cell Biol. 175, 791–802.
Wolf, K., Mazo, I., Leung, H., Engelke, K., von Andrian, U.H., Deryugina, E.I., Strongin, A.Y., Brocker, E.B., Friedl, P., 2003. Compensation mechanism in tumor cell migration: mesenchymal-amoeboid transition after blocking of pericellular proteolysis. J. Cell Biol. 160, 267–277.
Wright, D.E., Wagers, A.J., Gulati, A.P., Johnson, F.L., Weissman, I.L., 2001. Physiological migration of hematopoietic stem and progenitor cells. Science 294, 1933–1936.
Yamashita, S., Miyagi, C., Carmany-Rampey, A., Shimizu, T., Fujii, R., Schier, A.F., Hirano, T., 2002. Stat3 controls cell movements during zebrafish gastrulation. Dev. Cell 2, 363–375.
Yamashita, S., Miyagi, C., Fukada, T., Kagara, N., Che, Y.S., Hirano, T., 2004. Zinc transporter LIVI controls epithelial–mesenchymal transition in zebrafish gastrula organizer. Nature 429, 298–302.
Yu, S.R., Burkhardt, M., Nowak, M., Ries, J., Petrasek, Z., Scholpp, S., Schwille, P., Brand, M., 2009. Fgf8 morphogen gradient forms by a source-sink mechanism with freely diffusing molecules. Nature 461, 533–536.