Control of cell migration during *Caenorhabditis elegans* development

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In *Caenorhabditis elegans*, cell migration is guided by localized cues, including molecules such as EGL-17/FGF and UNC-6/netrin. These external cues are linked to an intracellular response to migrate, at least in part, by CED-5, a homolog of DOCK180/MBC, and MIG-2, a Rac-like GTPase. In addition, metalloproteases are required for a cell migration that controls organ shape.

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Abbreviations

FGF	fibroblast growth factor
GEF	guanine nucleotide exchange factor
HOX	homeobox
MBC	myoblast city
SM	sex myoblast
TGFβ	transforming growth factor β
TSP	thrombospondin

Introduction

Cell migrations are crucial for animal development. A classic example is the migration of neural crest cells in vertebrate embryos. In addition, aberrant cell migrations can promote disease. One example is the metastasis of cells in advanced cancers. How cell migrations are controlled during normal development is perhaps best addressed with the genetic and molecular tools available in the nematode *Caenorhabditis elegans*, and in the fly *Drosophila melanogaster*. In this review, we focus on recent advances in *C. elegans* and provide references to parallel work in other organisms. For a general review of *C. elegans* cell migrations, see [1]; for a recent review of both *C. elegans* and *Drosophila* regulators of cell migration, see [2].

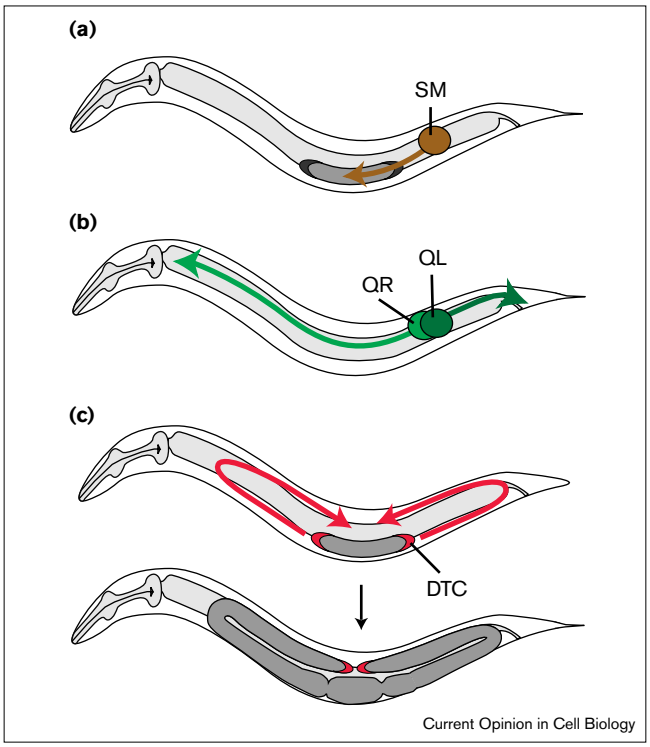
Two features of *C. elegans* make it particularly amenable to the analysis of cell migration controls. First, the animal is transparent and has a simple anatomy, making it possible to follow the migration of individual cells in the living animal throughout development. Second, migrations are invariant from animal to animal, so any deviations from the normal pattern can be detected. These features, together with its well-studied genetics [3], the complete sequencing of its genome [4••], and the ability to reduce gene function in this animal by RNA-mediated interference [5,6••], make *C. elegans* one of the best systems for analyzing cell migrations during development.

Certain cells in *C. elegans* have served as paradigms for controls of cell migration. These include the sex myoblast (SM), two Q neuroblasts (QL and QR) and their descendants, and the gonadal leader cells (Figure 1). In the following sections, we first describe recent progress on localized guidance cues (Figure 2), we then describe a possible link between these extracellular signals and the intracellular machinery driving cell motility, and finally describe an extracellular metalloprotease that is required for migration *per se* (Figure 3).

Fibroblast growth factor pathway

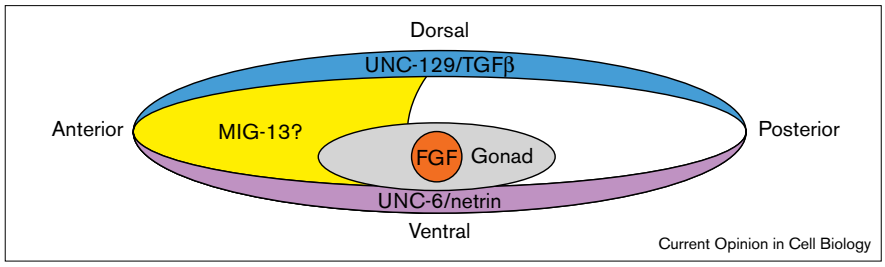
The fibroblast growth factor (FGF) receptor tyrosine kinase pathway has been implicated in numerous cell migrations during development, in both vertebrates and invertebrates [7–9]. In the *Drosophila* trachea and the vertebrate lung, FGF directs branching morphogenesis — a fundamental process that includes both cell migrations

Figure 1



Paradigms for cell migration in *Caenorhabditis elegans*. Animals are drawn from a lateral perspective. **(a)** Anterior migration of the sex myoblast (SM) towards the center of the developing gonad (arrow shows direction of migration). **(b)** Anterior migration (light green arrow) of QR and its descendants on the right side of the animal; posterior migration of QL (dark green arrow) and its descendants on the left. **(c)** Migration of gonadal leader cells (red arrows) to generate U-shaped gonadal arms.

Figure 2



Guidance of cell migrations in *Caenorhabditis elegans*. Schematic of the *C. elegans* body (larger oval) and gonad (smaller oval) in longitudinal section. EGL-17/FGF emanates from the central gonad (orange) as well as from the developing vulva (not shown); the SM cell uses EGL-17 to position itself in the center of the gonad. UNC-6/netrin is localized ventrally (purple); repulsion from UNC-6 drives migrating cells dorsally, whereas attraction to UNC-6 makes them migrate ventrally. UNC-129/TGFβ is localized in the dorsal region (blue) and influences migrations along the dorsal–ventral axis. MIG-13 is localized to the anterior and central domains of the animal (yellow); although MIG-13 affects the extent of anterior migrations, its role as a guidance cue is still speculative. See text for further explanation and references.

and cell shape changes. In *C. elegans*, FGF controls an apparently simpler process — migration of the SM towards the gonad.

The SM cell is born in the posterior of the animal during the first larval stage. In hermaphrodites, it migrates anteriorly to the central gonad and developing vulva, where it generates uterine and vulval musculature. Proper positioning of SM requires an FGF-like ligand encoded by the *egl-17* gene [10], and a receptor belonging to the FGF receptor subfamily, encoded by *egl-15* [11]. Mutations in either *egl-17* or *egl-15* cause SM migration to arrest before reaching the gonad. Significantly, the *egl-17* signaling ligand is expressed in both vulval and somatic gonadal cells ([12••]; CS Branda, MJ Stern, personal communication), and the *egl-15* receptor is expressed in the migrating SM cell [12••]. The idea is that the *egl-17* ligand is secreted by vulval and gonadal cells to form a signaling gradient that attracts and positions SM at the center of the gonad. A new component of the *egl-15/egl-17* pathway has been identified in a genetic screen for suppressors of loss-of-function *egl-15* mutations [13]. The *egl-15* suppressor, called *clr-1*, encodes a receptor tyrosine phosphatase and is thought to act as a negative regulator of receptor function; however, the mechanism of that negative regulation is not yet known.

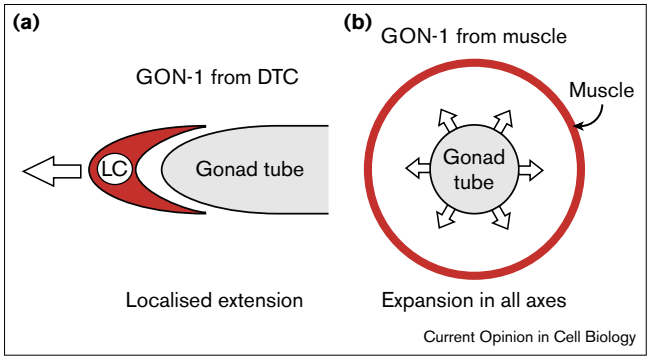
The control of SM migration provides a particularly simple example of guidance by FGF signaling. In other systems, FGF signaling is complicated by the existence of several rounds of FGF signaling, which control distinct cellular responses, and the existence of reciprocal signaling events [8]. Therefore, FGF signaling to the SM cell could be uniquely poised for more in-depth analyses of mechanism. How does activation of the EGL-17 receptor trigger cell movement? How is the FGF gradient generated? How is the gradient read so that the cell moves in a particular direction? The ability to manipulate this simple system may permit answers to these fundamental questions.

Homeobox (HOX) genes and Wnt signaling

Homeobox (HOX) transcription factors establish regional specificities in most animals (reviewed in [14]). In addition, HOX genes can regulate cell migrations in those body regions under their control [15,16,17••]. Perhaps the best example is control of the migration of Q neuroblasts and their descendants by *mab-5* (for a review see [15]). The *mab-5* HOX gene controls development in the mid-posterior body and, consistent with that function, *mab-5* is required for migration of QL toward the posterior but not for the anterior migration of QR. Normally, *mab-5* is expressed in QL, but not in QR [18]; furthermore, loss of *mab-5* expression in QL causes QL to migrate anteriorly, whereas ectopic expression of *mab-5* in QR causes QR to migrate posteriorly [18,19]. Similarly (but in a less well-understood fashion), another HOX gene *lin-39* regulates development in the central body region and influences anterior migration of QR in this region [20,21].

How is *mab-5* normally activated in QL but not in QR? These two neuroblasts occupy similar positions along the anterior–posterior axis and have equivalent ancestries in the embryonic lineage [22]. Recent work suggests that the difference resides in Wnt signaling [23••]. Mutations in the Wnt homolog *egl-20*, the Wnt receptor homolog *lin-17*,

Figure 3



Regulation of organ shape by the GON-1 metalloprotease. **(a)** Localized expression of GON-1 (red) in the leader cell (LC) allows migration and gonadal arm extension. **(b)** Expression of GON-1 by body wall muscle (red circle) allows uniform expansion of the developing gonad.

or the β-catenin homolog *bar-1* result in a loss of *mab-5* expression in QL. In contrast, a mutation in *pyr-1*, an inhibitor of Wnt signaling, results in ectopic expression of *mab-5* in QR [23••]. A major question is how Wnt signaling differentially activates *mab-5* expression in QL. One simple hypothesis is that the *egl-20* Wnt signal is asymmetrically distributed along the left–right axis.

Global guidance along the dorsal–ventral axis

Three *C. elegans* genes, *unc-5*, *unc-6*, and *unc-40*, are critical for dorsal–ventral migrations of both cells and axons [24]. A flurry of work since that classic paper has shown that these three genes belong to a system of guidance regulators whose sequence and function are conserved from worms to humans [25]. Best known are *C. elegans* UNC-6 and its vertebrate homolog netrin [26]. These laminin-related proteins are spatially restricted to the ventral region and are used to guide cell and axonal migration along the dorsal–ventral axis [27,28]. Both *unc-5* and *unc-40* encode cell surface receptors implicated in UNC-6-dependent migrations [29,30]. Intriguingly, the UNC-5 receptor promotes dorsal migration in response to netrin, whereas the UNC-40 receptor promotes primarily ventral migration in response to the same signal [24]. Work with these receptors in several organisms has recently shown that the key to this difference in the two receptors resides in their intracellular domains [31••,32••].

In a genetic screen for suppressors of ectopic netrin signaling in *C. elegans*, additional genes have been identified that function in dorsal–ventral guidance [33]. One such gene is *unc-129*, which encodes a member of the transforming growth factor β (TGFβ) superfamily [34••]. The *unc-129* gene is normally expressed dorsally and loss of UNC-129 function disrupts dorsal axon migration. In addition, forced misexpression of *unc-129* in the ventral musculature inhibits the dorsal migration of a different cell-type, the gonadal leader cells [34••]. This situation is reminiscent of that in *Drosophila*, where TGFβ signals also influence dorsal–ventral migration [7,35]. The use of both netrin and TGFβ signaling systems for dorsal–ventral guidance (Figure 2) could therefore be conserved. The existence of two systems for the same purpose could be used to reinforce guidance along the dorsal–ventral axis as well as to provide more flexibility in the regulation of these movements.

Global guidance along the anterior–posterior axis

In contrast to the dorsal–ventral axis, identification of a global guidance system for the anterior–posterior axis has been more elusive. Nonetheless, two components of such a system have recently been identified. The *vab-8* gene affects multiple posterior migrations [36], acts cell-autonomously and encodes a cytoplasmic protein with distant similarity to kinesin [37••]. Therefore, VAB-8 itself is not a guidance cue but is more likely to be involved in the cellular response to such cues. In contrast, the *mig-13* gene affects anterior migrations [19], acts non-autonomously and encodes a novel transmembrane protein [17••]. Expression of *mig-13* is normally restricted to the anterior and central regions of the animal (Figure 2) [17••] but uniform expression of *mig-13* can rescue migration towards the anterior nonetheless. Therefore, either MIG-13 is not itself a directional cue or its activity requires some other component localized to the anterior. Interestingly, the dose of MIG-13 appears to affect the extent to which cells migrate toward the anterior [17••]. Such a dose-dependence of MIG-13 might explain how cells migrating along the anterior–posterior axis are stopped at specific points along the body axis that are not associated with any known cellular landmark.

The intracellular response to signals directing cell migration

How are guidance cues translated by the cell to achieve cell migration? Small Ras-like GTPases, including Rho, Rac and Cdc42, are part of the cellular machinery required for remodeling the actin cytoskeleton and generating membranous extensions such as those at the leading edge of a migrating cell [38]. The significance of these small GTPases for cell migration and axon outgrowth has been confirmed in *C. elegans* [39], *Drosophila* [40,41] and mouse [42]. In *C. elegans*, the function of Rac has been examined using both null and activated forms of the Rac-like GTPase encoded by *mig-2* [39]. Intriguingly, the activated form inhibited cell migration in numerous cells, including the Q neuroblasts, whereas the absence of *mig-2* resulted in a decrease in the rate of migration of a subset of affected cells. Redundancy is the simplest explanation of this result. A second *C. elegans* gene critical for cell migrations, *unc-73*, encodes a guanine nucleotide exchange factor (GEF) that can activate Rac [43••]. As the expression patterns of *unc-73* and *mig-2* overlap, the *mig-2* GTPase might be a native target of the *unc-73* GEF.

An exciting new link in the Rac story comes from analysis of the *C. elegans* cell death gene, *ced-5*. Mutations in *ced-5* affect two seemingly different processes: engulfment of cell corpses after programmed cell death and gonadal leader cell migration [44••]. The *ced-5* gene encodes an ortholog of the mammalian DOCK180 and *Drosophila* myoblast city (MBC) proteins. This class of protein physically interacts with an adaptor protein called c-CRKII [45], which has been implicated in the control of cell migration [46]. Recently, DOCK180 has been found to interact directly with the GTPase Rac *in vitro* [47,48] and MBC appears to act in concert with Rac *in vivo* to influence cell shape [48]. Therefore, the CED-5/DOCK180/MBC family might provide a crucial link between the extracellular environment and intracellular regulators of cell shape and motility.

Metalloproteases and cell migration

Migrating cells often pass through a barrier of extracellular matrix and therefore matrix-degrading enzymes have been predicted to play a key role in cell migration [49]. Direct evidence for a role of metalloproteases in cell migration *in vivo* has been lacking until recently.

At least two metalloproteases control migration of the gonadal leader cells in *C. elegans* ([50••,51••,52]; K Nishiwaki, personal communication]. These migratory leader cells control formation of the extended U-shaped gonadal arm. Leader cell migration and arm extension occur within the confines of a basement membrane, which must be remodeled during migration and extension. The *gon-1* gene is crucial for migration of the gonadal leader cells [50••]. In wild-type animals, the leader cells migrate hundreds of microns, whereas in *gon-1(0)* null mutants, the leader cells do not move at all. The *gon-1* mutants also have defects in gonadogenesis unrelated to leader cell migration [50••], suggesting that *gon-1* might play at least two roles in gonadogenesis.

The *gon-1* gene encodes a secreted metalloprotease of a small family characterized by both a metalloprotease domain and one or more thrombospondin (TSP) type 1 repeats [51••]. The TSP type 1 repeats are likely to anchor GON-1 to the extracellular matrix and thereby localize its metalloprotease activity. A *gon-1* reporter transgene is expressed in both leader cells and body wall muscle [51••]. Expression of *gon-1* from different promoters has dramatically different effects on gonadal shape. When *gon-1* is expressed in the leader cells of a *gon-1(0)* mutant, their migration is rescued and gonadal arms extend normally. By contrast, when *gon-1* is expressed in muscle of a *gon-1(0)* mutant, no leader cell migration is observed but instead the gonadal tissues expand uniformly along all axes. Therefore, leader cell expression provides a localized activity essential for leader cell migration, whereas muscle expression provides a more dispersed activity required for uniform tissue growth (Figure 3). Although the GON-1 target is not yet known, one possibility is that GON-1 cleaves components of the extracellular matrix, a process that permits both migration through that matrix and tissue expansion. This idea is consistent with cleavage of collagen and the proteoglycan aggrecan by two vertebrate GON-1 homologs, procollagen I N-proteinase [53] and aggrecanase [54], respectively. Alternatively, GON-1 may cleave regulators that permit cell migration and tissue growth.

The *mig-17* gene (K Nishiwaki, personal communication), encodes a second metalloprotease involved in migration of the gonadal leader cell. Unlike *gon-1*, which is required for cell migration *per se*, *mig-17* influences the route of migration: in *mig-17* mutants, cells migrate in an unguided fashion [52]. Although the role of *mig-17* in cell migration is not yet understood, it might function in processing guidance cues or for interactions of the leader cells with their substrate as they migrate.

Conclusions and future directions

Cell migration is controlled by a combination of guidance cues, their receptors and the intracellular machinery responsible for driving cell movement. In addition, metalloproteases can influence cell migration and organ morphogenesis. Although the identification of these various migration regulators represents a major advance, many gaps remain in our understanding. It is of utmost importance to forge the link between the extracellular molecules that regulate migrations and the molecules that execute the motility response. That link has not yet been made, but is now approachable with the tools currently available both *in vitro* and *in vivo*.

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