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Zebrafish germ cells: motility and guided migration

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In the course of embryonic development, the process of cell migration is critical for establishment of the embryonic body plan, for morphogenesis and for organ function. Investigating the molecular mechanisms underlying cell migration is thus crucial for understanding developmental processes and clinical conditions resulting from abnormal cell migration such as cancer metastasis. The long-range migration of primordial germ cells toward the region at which the gonad develops occurs in embryos of various species and thus constitutes a useful *in vivo* model for single-cell migration. Recent studies employing zebrafish embryos have greatly contributed to the understanding of the mechanisms facilitating the migration of these cells *en route* to their target.

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Introduction

The function of organs relies on the arrangement and joint action of different types of cells that cooperate in performing the specific task fulfilled by the organ. In many cases, cells that build an organ originate at locations distant to the site at which the organ is destined to form and therefore to reach it, they have to migrate [1•,2,3]. Understanding the mechanisms controlling the precise migratory path of cells toward distinct sites within a 3-dimensional embryo is thus essential for understanding not only organogenesis but also the basis for clinical conditions that stem from impaired migration of cells [4,5]. In model organisms such as the mouse, *Drosophila* and zebrafish, primordial germ cells (PGCs) are specified in different locations in the embryo and migrate toward the location where the gonad develops, the site where they eventually differentiate into gametes, sperm and egg [1•,6,7]. PGCs migrate long distances within an embryo to reach the target and as such, they serve as an excellent *in vivo* model for investigating the mechanisms governing long-range cell migration.

Following their specification during early embryonic stages, PGCs polarize and acquire motility [8,9]. As they migrate, PGCs are presented with attractive and repulsive guidance cues provided by somatic cells along the migration path [1•,6]. For example, a key attractant for mouse and zebrafish PGCs is the chemokine Cxcl12 (Cxcl12a in zebrafish), which functions upon binding its receptor Cxcr4 (Cxcr4b in zebrafish) in directing the cells to their target [10,11]. As demonstrated in zebrafish, the correct level of Cxcl12a and the dynamic changes in its distribution require the decoy chemokine receptor, Cxcr7b [12]. Similarly, in *Drosophila*, PGCs are attracted toward the somatic part of the gonad by a lipid chemoattractant produced at the target region by the action of the HMGcoA reductase pathway [13]. Repulsive cues for PGCs in *Drosophila* rely on the function of lipid phosphate phosphatase enzymes (termed Wunens), which are expressed in regions of the embryo that PGCs avoid [14,15].

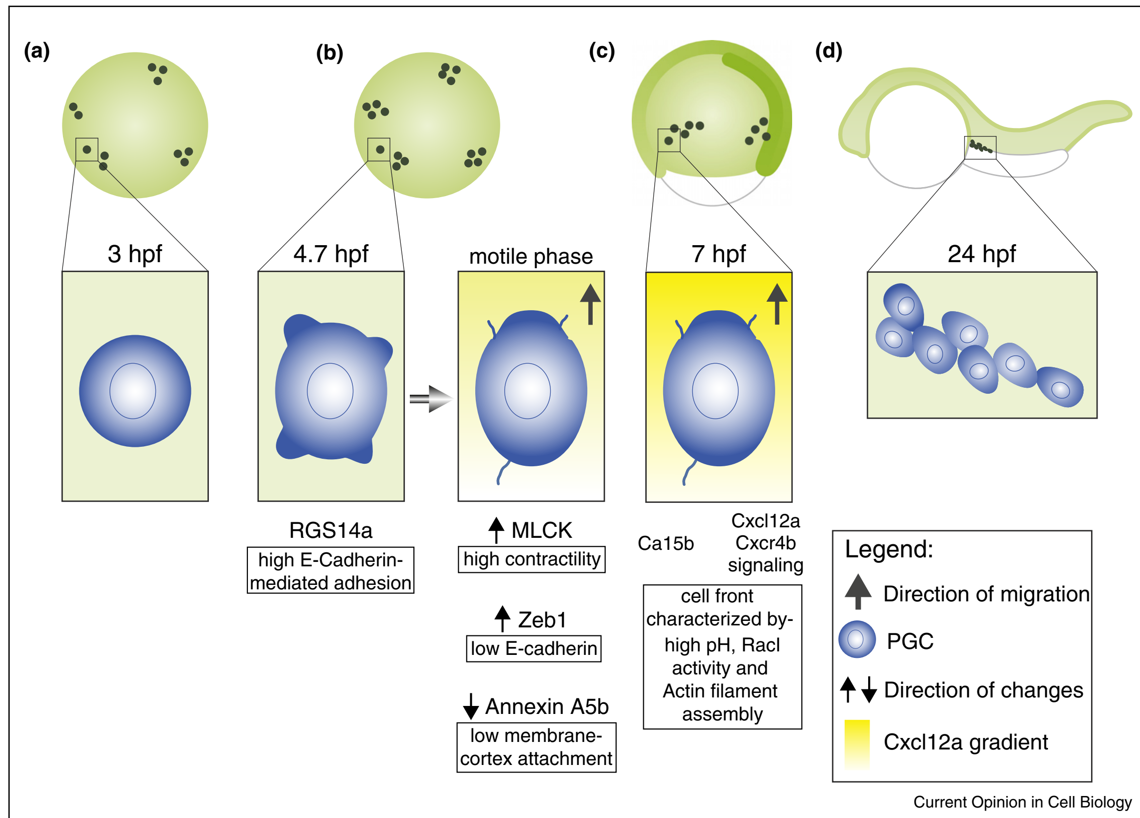
Directed by the guidance cues, *Drosophila* PGC migration on the correct track involves formation of cellular structures, termed pseudopodia, that is driven by actin polymerization [16]. PGCs explanted from *Xenopus* embryos on the other hand, exhibit bleb-like protrusions [17] that appear to be powered by cytoplasmic flow rather than by actin polymerization [18]. Likewise, zebrafish PGC migration is facilitated by the formation of actin-free protrusions in the form of blebs that are inflated in the direction of migration [19]. This mode of migration is similar to that exhibited by different migrating tumor cells *in vitro* [20,21]. The biased formation of blebs in the direction of migration is governed by the polar activation of Cxcr4b around the cell circumference, that defines a stable leading edge characterized by enhanced activation of the small RhoGTPases, RhoA and Rac1 [18,19,22].

In this review we summarize the current understanding of the developmental and cellular mechanisms facilitating the arrival of zebrafish PGCs at their target during early embryogenesis (Figure 1) and present directions for future research on this topic.

Timing of cell motility

Tight control over the timing of the initiation of migration is critical for a range of biological processes, allowing the coordination of many events in development and homeostasis [23–25]. Indeed, abnormal regulation of cell

Figure 1



Steps of zebrafish PGCs migration. **(a)** At 3 hpf, zebrafish PGCs are found in four cell clusters within the embryo and show a round morphology and lack of motility. **(b)** At 4.7 hpf, the PGCs start generating protrusions in all directions while remaining immotile as a result of the expression of the RGS14a protein and a high level of E-cadherin. Concomitant with the establishment of Cxcl12a gradient, an elevation in contractility, a reduction in E-cadherin level and a reduction in the level of membrane-cortex attachment facilitate cell motility and polarization, which is also manifested in polarized filopodia formation. **(c)** In response to Cxcl12a gradients the cells establish high pH levels at the cell front, in a process requiring the function of Ca15b and filopodia. The polar pH distribution facilitates an elevation in Rac1 activity and enhanced Actin filament assembly at the cell front. **(d)** By the end of the first day of development the PGCs cluster at the region where the gonad develops.

motility is at the basis of medical conditions such as cancer metastasis [26].

Following their specification at 3 hours post fertilization (hpf), zebrafish PGCs are round and immotile (Figure 1a). Subsequently, the PGCs undergo morphological changes characterized by generation of protrusions in all directions followed by a polarized extension of blebs in the direction of migration and the onset of motility around 5 hours into embryonic development [8] (Figure 1b). These changes in cell shape depend on the function of the RNA-binding protein Dead end (Dnd) [27] and are correlated with a decrease in the level of the cell adhesion molecule E-cadherin on the surface of the cells [8,28••]. The actual acquisition of PGC motility is thus halted after their early specification. This delay effectively coordinates the change in cellular features of PGCs with the initiation of *cxcl12a* transcription by differentiating mesodermal cells at around 5.3 hpf [29••]. Suspending the onset of cell migration maintains the cells at the site of specification that is in the vicinity of initial *cxcl12a* expression domains. This course of events reduces the chances of PGCs migrating away from sites of the chemokine attraction, thereby ensuring the arrival of all the cells at their final target by the end of the first day of development. The regulator of G-protein signaling 14a (Rgs14a) is a molecule that participates in controlling the timing of PGC migration initiation in this context. RGS14 functions by attenuating the signaling activity of G-proteins by acting as a GTPase activating protein (GAP), increasing the rate of conversion of the GTP to GDP. *rgs14a* was identified in a screen for RNAs expressed in early PGCs and similar to other RNAs important for germ-cell development (e.g. *nanos* [30,31] and *dnd* [27]), *rgs14a* RNA is localized to the germ plasm [29••]. Consistent with a function as a protein inhibiting premature migration, *rgs14a* level gradually decreases until the onset of PGC motility [29••]. Interestingly, in dendritic cells and B

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