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# Finding their way: themes in germ cell migration

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Embryonic germ cell migration is a vital component of the germline lifecycle. The translocation of germ cells from the place of origin to the developing somatic gonad involves several processes including passive movements with underlying tissues, transepithelial migration, cell adhesion dynamics, the establishment of environmental guidance cues and the ability to sustain directed migration. How germ cells accomplish these feats in established model organisms will be discussed in this review, with a focus on recent discoveries and themes conserved across species.

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## Introduction

Embryonic development involves the complex and coordinated movement of many cell types. In many metazoans, germ cells are specified at one location in the embryo and must translocate across a large distance to find the developing somatic gonad. This translocation often involves more than one process, including moving passively with underlying somatic cells, traversing epithelial barriers and responding to environmental guidance cues during active migration. As defects in any one of these processes can compromise fertility, the migration of germ cells is a critical component of the germline lifecycle and propagation of many metazoan species. As such, germ cell migration has been the subject of intense scientific interest for more than one hundred years [1–3] and has yielded a wealth of insights into the mechanisms of cell migration in the context of dynamically developing embryos. This review will focus on recent discoveries and highlight features and strategies shared by many model organisms.

## Migratory paths of germ cells

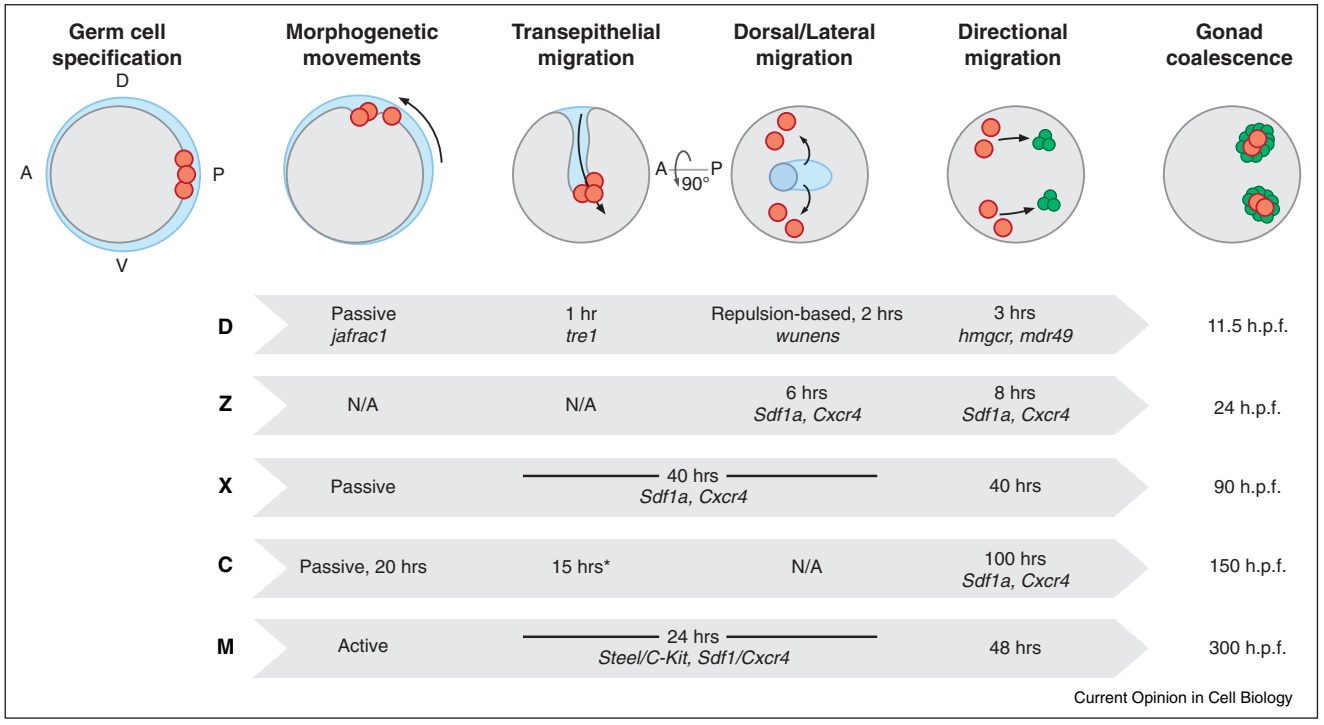
Germ cell migration is investigated in an ever-growing number of organisms [4,5••,6,7]. Established model organisms include mice, chicken, frogs, fruitflies and two teleost fish: zebrafish and medaka [8,9•,10–13]. Despite divergence, features of overall path of embryonic germ cells can be remarkably similar between these species. For instance, germ cells are often specified at the posterior edge of the embryo or at the border between embryonic and extraembryonic tissues (Figure 1). Germ cells then translocate during morphogenetic movements. These movements usually occur during gastrulation and involve movements with endodermal tissue toward the center of the embryo. In Drosophila and Xenopus, the translocation with endodermal tissue is a passive process and known to require germ cell adhesion to underlying endodermal epithelium [14,15], while germ cell morphology suggests that endoderm translocation may be an active process in mice [16,17]. Germ cells that get enclosed within the developing endoderm must undergo a transepithelial migration to enter the mesoderm before migrating both dorsally and laterally to form two groups of germ cells that will occupy each somatic gonad. In Drosophila and mice, these dorsal/lateral movements occur after gut exit, while in Xenopus the dorsal/lateral movements occur before endoderm exit [10,14].

Alternative migration paths are observed in two model organisms. In chicken embryos, germ cells translocate through the vasculature before migrating along the dorsal mesentery toward the developing somatic gonads [18]. In zebrafish, germ cells do not appear to enter the endoderm and because they are specified at four random locations, do not have to bilaterally sort in order to form two separate groups [19]. Instead, zebrafish germ cells migrate dorsally to occupy a large zone along the dorsal midline and only a portion of germ cells migrates laterally [19,20]. Despite these unique features, all germ cells studied in depth seem to undergo an active migration guided by attractive and repulsive cues toward the genital ridges or somatic gonadal precursors of the developing gonad. Somatic gonadal cells and germ cells then coalesce to form the complete embryonic gonad. The mechanisms by which germ cells navigate several tissue types in order to reach the gonad are often similar in many organisms and will be discussed in further detail.

## Transepithelial migration

Germ cells in many species must cross an epithelium to reach the gonad. Insights into how germ cells traverse this barrier have been made through studies in mice and Drosophila. Several signal transduction pathways have

**Figure 1**




Shared themes in the migration path of embryonic germ cells. Shown are highly stylized schematics of an embryo not meant to represent any one species. The 'species-less' embryo is shown at six key events during germ cell migration in chronological order from left to right. First, germ cells (red) are specified, often at the posterior or edge between embryonic (gray) and extra-embryonic (blue) tissue. Second, germ cells move during somatic morphogenetic movements (dashed arrow). In many species, germ cells move passively during gastrulation and often move within the developing mid or hindgut. Third, germ cells in several species undergo a transepithelial migration to exit the gut. Fourth, germ cells move dorsally and laterally, sorting into two populations. Fifth, germ cells undergo a sustained, directed migration toward the developing somatic gonad (green circles). Sixth, germ and somatic gonadal cells coalesce to form the complete embryonic gonad. Shown underneath each stage of germ cell migration is a table with characteristic, key factors and length of stage noted for specific model organisms: D, Drosophila; Z, zebrafish; X, Xenopus; C, chicken; M, mouse; Hpf, hours post fertilization; A, anterior; P, posterior; D, dorsal; V, ventral. *Unlike other species, chicken germ cells migrate through the vascular epithelium rather than the gut epithelium.

been implicated in mouse germ cell exit from the hindgut, including Fibroblast growth factor (FGF) [21], Wnt [22] and Transforming growth factor beta (TGF-β) [23,24]. Which cells produce and respond to these signals has yet to be determined, though the TGF-β responsive gene *foxc1* is expressed in the mouse hindgut, suggesting a non-autonomous role for germ cell exit [24]. FGF signaling facilitates germ cell exit in both mice and Drosophila. In mouse explants, the addition of FGF2 causes germ cells to exit the explanted gut with increased velocity [21]. In Drosophila, FGF signaling is required for dynamic E-cadherin localization within the endodermal epithelium to prevent a midgut collapse that traps germ cells [25••]. Together, these findings suggest that germ cells require a dynamic gut epithelium for a properly timed germ cell exit. Strong support for this postulate was recently found in Drosophila. By genetically manipulating the timing of endodermal remodeling, it was demonstrated that an endodermal epithelial to mesenchymal transition is both necessary and sufficient for germ cell migration out of the midgut (Figure 2) [26]. Thus, at least in some organisms, germ cells rely on epithelial dynamics to traverse barriers.

## Adhesion dynamics

Changes in adhesion are often observed in germ cells during endodermal exit or the initiation of active migration. The cell–cell adhesion protein E-cadherin is dynamically regulated in germ cells in many organisms (Figure 2). In zebrafish, E-cadherin is downregulated in migratory germ cells by the depletion of *regulator of G-protein signaling 14a* (*Rgs14a*) [27,28]. Similarly, recent studies of isolated Xenopus germ cells using single cell force spectroscopy have shown that isolated migratory Xenopus germ cells have less E-cadherin-mediated adhesion capabilities compared to isolated pre-migratory Xenopus cells [28,29,30•]. Interestingly, mouse germ cells display an increase in E-cadherin expression during exit from the hindgut, although mouse E-cadherin does not appear to be strictly required for migration to the somatic