A pilgrim's progress: seeking meaning in primordial germ cell migration

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Abstract

Comparative studies of primordial germ cell (PGC) development across organisms in many phyla reveal surprising diversity in the route of migration, timing and underlying molecular mechanisms, suggesting that the process of migration itself is conserved. However, beyond the perfunctory transport of cellular precursors to their later arising home of the gonads, does PGC migration serve a function? Here we propose that the process of migration plays an addition role in quality control, by eliminating PGCs incapable of completing migration as well as through mechanisms that favor PGCs capable of responding appropriately to migration cues. Focusing on PGCs in mice, we explore evidence for a selective capacity of migration, considering the tandem regulation of proliferation and migration, cell-intrinsic and extrinsic control, the potential for tumors derived from failed PGC migrants, the potential mechanisms by which migratory PGCs vary in their cellular behaviors and corresponding effects on development. We discuss the implications of a selective role of PGC migration for in vitro gametogenesis.

Graphical abstract
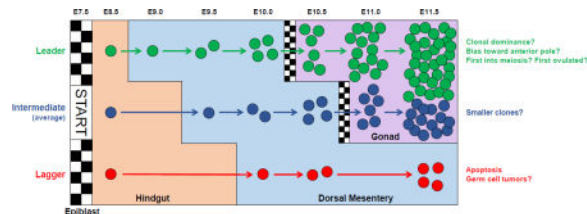
Keywords

primordial germ cell; migration; cell competition; germ cell tumor; germ cell selection

Throughout human history, journeys to sacred places have been undertaken in search of clarity, health, or successful reproduction. Pilgrims to Wutai Shan Mountain in Mongolia

sought rebirth in a womb-like cave (Charleaux 2011); on Isla Mujeres, the sanctuary of the fertility goddess Ixchel first drew the ancient Mayans (McKillop 2004); travelers on the Camino de Santiago de Compostela in Spain carried a scallop shell, a symbol of fertility, as their badge (Wikipedia, 2016). In a striking parallel, fertility itself hinges upon a journey of cells across the developing embryo in many diverse organisms. Primordial germ cells (PGC) are among the first lineages established in development, and the successful passage of these dedicated precursors from their birthplace to the gonad primordia ensures an adequate supply of gametes for reproduction in the adult (McLaren 2003; Kunwar *et al.*, 2006; Wong *et al.*, 2013).

The study of PGC development in flies, fish, birds, amphibians and mammals reveals surprising diversity in the migratory circuits as well as the underlying molecular mechanisms. Migration initiates from the embryo posterior in most organisms; however, avian PGCs begin in the anterior germinal crescent (Nakamura *et al.*, 2007). Transit through epithelial sheets of the endoderm is common to rodents, *Xenopus*, and *Drosophila*, and interstitial movement through mesoderm occurs in zebrafish, mammals, and *Drosophila* (Figure 1; Kamimura *et al.*, 1976; Kunwar *et al.*, 2006; Raz, 2004). Whereas fish PGCs move in clusters during gastrulation, this is the exception, as PGCs in most organisms move as single cells, with an extreme example as chick PGCs homing through the vasculature similar to lymphocytes (Nakamura *et al.*, 2007). Common expression of the PIWI family of genes and RNA helicases such as VASA in PGCs of most organisms suggests that the cell lineages are homologous, in spite of differing modes of specification (Hay *et al.*, 1990; Yoon *et al.*, 1997; Megosh *et al.*, 2006; Juliano *et al.*, 2010); however, there is no such ancient molecular guidance system specific to PGCs. Rather, mechanisms of chemoattraction and repulsion appear to have been borrowed by PGCs from blood cells, neurons, and mesoderm (Richardson and Lehmann, 2010). Together these observations suggest that it is PGC migration itself that has been conserved during evolution rather than specific mechanisms (Figure 1).

Why does PGC development across so many phyla involve a pilgrimage within the embryo? Whether germline fate is acquired by inheritance of cytoplasmic determinants or inductive signals delivered to pluripotent cells (Extavour and Akam, 2003), the early specification of PGCs mandates a strategy for awaiting organogenesis and transiting to their eventual home of the gonad. Thus, migration fulfills this perfunctory requirement, but does it serve a function beyond transport? Here we propose that the process of migration plays an additional role in germline quality control. We suggest that negative selection occurs via elimination of PGCs incapable of completing migration as well as through mechanisms that favor PGCs capable of responding appropriately to migration cues. In this review, we will explore evidence for a selective capacity of migration, focusing primarily on PGCs in mice.

1 The yin and yang of mouse PGC migration

Mouse PGCs are specified from epiblast at E7.5, travel within the growing hindgut epithelium, then egress through the mesentery before colonizing the emerging gonads by E11.5 (Figure 1; Saitou, 2012). Only after this point does sex-specific differentiation proceed as PGCs, now termed gonocytes, enter meiosis in females and mitotic arrest in

males at ~E13 (Chiquoine, 1954; McLaren, 2003). While undergoing migration, these PGCs are also coordinating other cell processes important for their development, including epigenetic reprogramming and expansion. Distinct from other model organisms in which proliferation follows migration (Su *et al.,* 1998; Richardson and Lehmann, 2010; de Melo Bernardo *et al.*, 2012), mammalian PGCs are actively proliferating during their migration, increasing in population size from approximately 45 cells at E7.5 to ~200 at E9.5 (Saitou *et al.*, 2002; McLaren, 2003; Seki *et al.*, 2007), ~2500 at E11.5 (Laird *et al.,* 2011), and peaking around 25,000 at E13.5 (Tam and Snow, 1981).

1.1 Regulation of PGC migration by intrinsic versus extrinsic signaling mechanisms

PGCs are a unique model for parsing the effects of intrinsic and extrinsic signaling owing to their known interaction with a diversity of cell types as they move from their point of specification in the epiblast to their ultimate residence in the gonads. The mammalian germline is particularly interesting due to the multitude of cellular processes that take place concurrently with PGC migration – proliferation, survival, and epigenetic reprogramming (reviewed in Ewan and Koopman 2010). This complexity of development across several, distinct microenvironments has generated many questions regarding the role of the soma in regulating PGC development. Previous work identified a requirement for *KitL* as well as *Sdf1* (also known as *Cxcl12*) from somatic cells in regulating PGC survival and proliferation while simultaneously guiding their movement in mice (Gu *et al.*, 2009; Gu *et al.*, 2011; Runyan *et al.*, 2006; Ara *et al.*, 2003; Molyneaux *et al.*, 2003). Both factors provide chemotactic and survival signals; thus, loss of *KitL, Sdf1*, or their respective receptors, *cKit* and *Cxcr4*, leads to inefficient colonization of the gonads and diminished numbers of PGCs.

More recently, the non-canonical Wnt receptor *Ror2* and its main ligand *Wnt5a* were implicated in the migration of PGCs by a forward genetic screen in mice (Laird *et al.*, 2011; Chawengsaksophak *et al.*, 2012). In contrast to the temporal and spatial restriction to PGCs of the receptors *cKit* and *Cxcr4*, *Ror2* is expressed on both PGCs and their somatic cell neighbors, most highly in the hindgut epithelium, and at lower levels in the dorsal mesentery and gonadal ridges. In PGCs, *Ror2* provides autonomous control of motility, as evidenced by an increase in the number of germ cells remaining outside the gonadal ridges at the conclusion of migration in both the *Ror2^{Y324C}* full loss-of-function mutant and the PGC-specific *Ror2^{cKO}* mutant (Laird *et al.*, 2011; Cantú *et al.*, 2016; Cantú and Laird, unpublished results). Another autonomous function for *Ror2* is in the regulation of PGC proliferation, with aberrantly high rates of cycling PGCs found in the hindgut of both ubiquitous and PGC-specific mutants (Cantú *et al.*, 2016). However, unlike the persistence of motility defects in *Ror2* mutants for the duration of PGC migration, the specificity of proliferation phenotypes implies that the control of the PGC cell cycle by *Ror2* signaling is limited to a single somatic compartment. This suggests that mitogenic signals from the microenvironment differ between somatic compartments, while the factors that enable PGC movement are more stable and consistent. The high level of WNT5a in the hindgut compared to the surrounding mesentery is the most likely basis for this location-specific phenotype, but does not explain the absence of proliferation defects in the gonadal ridges, where WNT5A is also high. Other secreted factors such as SFRP1 may regulate the availability of Wnt ligands or alter the balance of signaling in a compartment-specific

manner. Future studies to profile mitogenic regulators specific to each somatic niche will be needed to test this hypothesis. Furthermore, given the high level of expression, the possible function of *Ror2* in the PGC niche remains to be identified.

The work described above takes a PGC-centric view in assessing the interactions between the germline and the soma. However, evidence from other species suggests that contact between PGCs and their somatic neighbors can be mutually beneficial for the development of both tissues. In the human embryo, PGCs and nerve fibers colonize the gonadal ridges at the same time (Møllgård *et al.*, 2010). Image analysis shows human PGCs in the dorsal mesentery to the gonadal ridges in close association with developing nerve fibers and Schwann cells, and intriguingly PGC chemoattractants such as *KitL* (Høyer *et al.*, 2005), and *Sdf1* (Belmadani et al. 2005) are expressed in the developing nervous system. While Møllgård and colleagues conclude that the nervous system guides the PGCs to the gonads, one might speculate that the interplay between the cell types is more complex. Migratory PGCs in *Drosophila* have been found to regulate and direct the movement of the caudal visceral mesoderm (CVM), progenitors of the midgut muscles, a neighboring cell type that shares a common migratory route with PGCs (Stepanik *et al.*, 2016). Live imaging in PGC migration mutants found that CVM cells exhibit an affinity for PGCs and will invade inappropriate tissues to localize with mismigrated germ cells. When PGCs are absent, CVM migratory behavior is altered, resulting in muscle defects in the midgut. Although migratory PGCs in *Drosophila* influence the development of their microenvironment, a similar education of the somatic tissues by PGCs has not yet been identified in the mouse. Thus far, it seems that embryogenesis occurs normally in the absence of PGCs (Mintz and Russell 1957; Chen *et al.*, 2013; Hayashi *et al.*, 2011); however, the development and movement of the somatic cell types that comprise the migratory route during PGC migration have yet to be comprehensively characterized.

1.2 Cell migration versus proliferation

In many organisms, the period of PGC migration is distinct from their proliferation, with migration following initial specification and proliferation commencing upon arrival in the gonads (reviewed in Richardson and Lehmann 2010). The mammalian system, however, is an exception. In the mouse embryo, PGCs begin dividing as soon as they are specified and continue to expand in population size until meiotic entry in the female or mitotic arrest in the male (Tam and Snow 1981; Seki *et al.*, 2007). This concurrence of migration and proliferation is surprising based on the differences in cell morphology and adhesion each process requires; elongation, formation of protrusions, and dynamic adhesions with the microenvironment during migration would appear to be at odds with the rounding up and loss of adhesion that occur during proliferation.

In general, the ability of actively migrating cells to divide is not unusual; neural crest cells and lateral line primordium in zebrafish proliferate during their embryonic migrations (Huszar *et al.*, 1991; Laguerre *et al.*, 2005; Ciruna *et al.*, 2006). However, these cell types utilize collective cell migration rather than migrating singly like PGCs, and it is likely that passive movement of cells within the group is more compatible with dividing, effectively eliminating interruptions in their migration. PGC motility and the cell cycle are much more

likely to be conflicting processes, requiring that the cell choose one at the expense of the other. We see this antagonism most clearly at the period of active PGC migration – invasion through the basement membrane and egress from the hindgut. In this specific microenvironment, PGC proliferation is most strongly suppressed (Cantú *et al.*, 2016), allowing cells to be more highly motile. We further showed that these dueling cell functions are regulated by antagonism between two arms of the Wnt pathway, where noncanonical *Wnt5a-Ror2* signaling promotes cell motility while inhibiting *β-catenin*-mediated proliferation. Additionally, *Ror2*-mutant PGCs are more rounded in shape, likely as a result of increased cell division, akin to what we observe in the highly proliferative gonadal ridge (Laird *et al.*, 2011). Thus, we propose that the antagonism is mutual – in mutants with higher rates of proliferation, such as $Ror2^{Y324C}$ and $βcat^{GOF}$, there is a migratory delay (Laird *et al.*, 2011; Cantú *et al.*, 2016). In support of these findings in PGCs, suppression of canonical Wnt signaling by the noncanonical Wnt pathway has been found in neuronal migration during *C. elegans* development as well as several cell lines (Forrester *et al.*, 2004; Mikels and Nusse 2006; Mikels *et al.*, 2009), although downstream effectors remain unknown.

The conflict between migration and proliferation of PGC was also described in the developing reproductive tract of *C. elegans*, where the anchor cells are only capable of invading into the vulval epithelium during G1/G0 cell cycle arrest (Matus *et al.*, 2015). Induction of proliferation in these normally quiescent cells blocks their invasive function. While this model is unique in that the anchor cells are not migratory – they breach the basement membrane with protrusions but do not translocate the cell body – these findings have implications for other highly invasive cell types such as metastatic cancers. Using experimental data, *in silico* modeling of the interplay between migration and proliferation of cancer cells predicts that highly proliferative cells have impaired movement when confronted with limited metabolic resources and physical barriers than their less proliferative counterparts (Hecht *et al.*, 2015). Traditional treatment of cancer in patients has targeted highly proliferative cells, potentially leaving behind quiescent and invasive cell populations. One such drug, Palbociclib (PD-0332991), directly targets the cell cycle by inhibiting the G1/S transition via CDK4/6 (Baughn *et al.*, 2006) and is currently being tested in clinical trials for many different cancers. While Palbociclib has shown great promise in blocking the cell cycle and suppressing tumor growth, it has also induced EMT and invasion in pancreatic cancer cell lines (Liu and Korc 2012). This raises the possibility that inhibition of proliferation in cancer may induce metastatic behavior. Thus, the antagonism between cell migration and proliferation could have severe consequences on the progression of human disease and patient outcomes.

1.3 *Wnt5a-Ror2* versus *KitL-cKit* signaling in PGCs

Because mammalian PGC migration remains largely understudied, most work thus far has focused on singular and specific signaling pathways, without much clear overlap. Our previous work on *Ror2* in the germline opened the door for examining the interactions between key pathways with the observation that *Ror2*-mutant PGCs are less responsive to *KitL* in terms of migratory morphology (Laird *et al.*, 2011). Based on the further characterization of PGC phenotypes in multiple models of *Ror2* loss ($Ror2^{Y324C}$, $Ror2^{-/-}$ and $Ror2^{cKO}$), we have uncovered distinct areas of separation and overlap between the

Wnt5a-Ror2 pathway and *KitL-cKit* signaling. In order to promote PGC motility, these pathways work together to induce cell elongation and polarity, general requirements for effective migration (Laird *et al.*, 2011). However, they diverge in the regulation of PGC proliferation and survival. *Wnt5a-Ror2* signaling can suppress proliferation in regions of high *KitL* expression, such as the E9.5 hindgut, which we demonstrated by the elevation of proliferation of *Ror2*-mutants in this microenvironment. We furthermore observed that germ cells manage to survive despite autonomous loss of *Ror2*, leading to an overall doubling of the PGC population in *Ror2^{cKO}* mutants compared to controls (Cantú and Laird, unpublished results). Without the current knowledge of *Ror2* phenotypes and potential interplay with *KitL-cKit*, initial studies of PGCs using combinations of genetic mutants in these pathways proved difficult to interpret. Return to this line of inquiry will be feasible with conditional alleles of each receptor, candidate downstream readouts, and emerging testable hypotheses about the function of each pathway in the motility, proliferation, and survival of PGCs.

2 Infidelities in germ cell migration

Molecular regulation of PGC migration in mice appears to be complex and redundant, which confers robustness, but comes with a downside: heterogeneity of cellular behavior. This complexity is evidenced by the changing cellular morphology and variety of different kinds of movements observed during the 5-day odyssey from PGC specification to colonization of the gonad. Redundancy in genetic control of PGC migration is suggested by the absence of mouse mutants in which migration of PGCs is completely disrupted. This includes spontaneous, targeted or chemically-induced mutants, and an ENU screen corresponding to ~10% of the genome (D. Laird, unpublished data). A consequence of multiple redundant processes operating simultaneously is fluctuation, and quantification of PGC location by embryonic age reveals a high degree of variability during the migratory period (Cantu *et al.*, 2016). By the conclusion of migration at E11.5, about 5% of PGCs remain outside of the gonads (Laird *et al.*, 2011), and these are eliminated by apoptosis (Runyan *et al.*, 2006).

The trigger for programmed cell death of PGCs that wander off route is believed to be the withdrawal from support factors, such as KitL (Dolci *et al.*, 1991; Matsui *et al.*, 1991; Godin *et al.*, 1991; Pesce *et al.*, 1993). Apoptosis of PGCs during the migratory period occurs via the intrinsic pathway (Stallock *et al.*, 2003; Rucker *et al.*, 2000); however, elimination of wayward PGCs can fail, as evidenced by their capacity to give rise to disorganized tumors known as teratomas that contain derivatives of all three germ layers. The PGC origin of testicular teratomas was demonstrated by abolishing tumors in a susceptible mouse strain by crossing to a *cKit* mutant, which lacks PGCs (Stevens 1967, 1974, 1984). Mutations in the oncogenes *Pten, CyclinD1, Dmrt1* and *Dnd1* have been shown to cause testicular teratomas in mice (Kimura *et al.*, 2003; Cook *et al.*, 2009; Krentz *et al.*, 2009; Heaney *et al.*, 2012) and variants in some of these loci are associated with the same tumors in humans (Litchfield *et al.*, 2015). The functions of these genes suggest that neoplasms from fetal gonocytes that fail to maintain proliferative arrest or resist differentiation (Peterson 2012). However this may be distinct from the origin of teratomas from PGCs that fail migration (Runyan *et al.*, 2008).

Teratomas are also found in other locations, including the spine and coccyx, mediastinum and even intracranially (Grosfeld 1985). With an occurrence of ~1 of every 30,000–40,000 live births, Saccrococcygeal Teratoma (SCT) is the most common tumor in newborns and young children, whereas it is exceedingly rare in adults (Rescorla 1998). The most likely source of extragonadal germ cell tumors is a lesion in a migratory PGC (reviewed in Looijenga 2013) because their predominance in midline structures correlates with the migration of PGCs through the hindgut and medial mesentery before bifurcating to the gonads (reviewed in Bustamante-Marin 2013). The not infrequent observation of PGCs left in these locations in wild-type mice after migration is complete argues that the PGC origin of SCTs is more feasible than from derivatives of the embryonic signaling center known as the node (Moore 2003) or as a result of somatic cells reacquiring pluripotency (Economou 2016). Although the presence of a latent pluripotency program in PGCs (Matsui 1992, Resnik 1992) might render them more susceptible to oncogenic transformation, concrete evidence linking SCTs to failed PGC migrants is lacking. Molecular characterization of SCTs in humans as well as the development of a mouse model are much needed in this field.

3. Germ cell quality and selection

Germ cell development is a lengthy and complex process that starts with specification in the early embryo and proceeds through stages of migration, proliferation, epigenetic reprogramming, sex differentiation, and gametogenesis to ultimately produce mature oocytes and sperm (reviewed in Ewan and Koopman 2010). Here we posit that each step following specification can potentially function as a selective mechanism to ensure that that highest quality germ cells become the adult gametes. Even though their migration occurs early in gametogenesis, PGCs could harbor defects that negatively impact later development and future progeny. Migratory PGCs may acquire genetic mutations resulting from rapid proliferation in the blastocyst prior to germline specification (MacAuley *et al.*, 1993). Recent measurement of mutation at one locus using the BigBlue mouse demonstrated a decrease in the mutational load in the germline as development proceeded, arguing for a process of selection against the most damaged germ cells; the overall decrease in germ cell mutational load as compared to somatic cell lineages could indicate a greater capacity for DNA repair in addition to negative selection in the germline (Murphey *et al.*, 2015).

Beyond integrity of the genome, precise control of epigenetic reprogramming is necessary to maintain PGC identity and function (reviewed in De Felici 2011). The process of genome-wide DNA demethylation that occurs during PGC development is not indiscriminate, as genes critical to post-migratory PGC function, imprinted genes, and retrotransposons remain highly methylated until after gonadal colonization (Maatouk *et al.*, 2006; Seisenberger *et al.*, 2012; Hackett *et al.*, 2012). Additionally, histone modifications that occur during migration, including erasure of *H3K9me2* and addition of *H3K27me3* and *H4/H2AR3me2*, appear to move the genome toward greater transcriptional plasticity while preventing inappropriate differentiation (Seki *et al.*, 2005; Ancelin *et al.*, 2006). It remains unclear whether this phase of epigenetic reprogramming is linked to PGC migration and movement through different somatic microenvironments or might be intrinsically regulated by developmental timing. Thus, selective mechanisms may be important for eliminating PGCs carrying aberrant epigenetic marks to preserve the integrity of the germline.

A mechanism relevant to selection during development is cell competition, which is an emergent behavior upon interaction between cells that express differing levels of certain proteins. Cell competition has been studied in the *Drosophila* embryo (wing imaginal disc) as well as the epiblast of the mouse embryo, both of which are epithelial tissues (Morata and Ripoll 1975; Clavería *et al.*, 2013). In these cases, heterogeneity between adjacent cells enables some with a greater ability to expand, via proliferation, and kill their weaker neighbors (Morata and Ripoll 1975; Moreno *et al.*, 2002; Clavería *et al.*, 2013). Thus, the surviving cells are considered to be more fit than their counterparts and go on to contribute a greater share of progeny to the developing tissue or organism (reviewed in Amoyel and Bach 2014).

It is easiest to imagine how cell competition might act in the developing gonads, where PGCs cluster in tight colonies (Tam and Snow 1981) and are close enough to outcompete and kill their neighbors. During the migratory period, however, PGCs are dispersed throughout multiple tissues as they move as single cells (Cantú *et al.*, 2016) and interaction between germ cells prior to gonadal colonization remains functionally unclear. Examination of PGCs in histological sections revealed contact between some germ cells via long and thin protrusions, potentially forming a network of distantly connected cells (Gomperts *et al.*, 1994). Additionally, it is known that gap junctions are required for early PGC development; embryos deficient in *Gja1* (known as *Connexin43*) exhibit a loss of germ cells at E11.5 as a result of migratory defects and increased apoptosis (Francis and Lo 2006). Cyst formation in PGCs via intercellular bridges begins at E10.5, prior to the conclusion of migration (Pepling and Spradling 1998; Lei and Spradling 2013; Greenbaum *et al.*, 2009). However, live imaging of germ cells in embryonic slice culture suggests that migratory PGCs make more brief contacts with each other before gonadal colonization (Molyneaux *et al.*, 2001). Also, PGC-PGC coupling was not directly observed in the *Connexin43* study, and it remains unclear if cyst formation at E10.5 occurs in all germ cells or specifically those already in the gonad and thus post-migratory (Francis and Lo 2006; Pepling and Spradling 1998; Lei and Spradling 2013).Given the conflicting results described above, we propose that any competition occurring at this stage of development would rely primarily on the fundamental and relative fitness of each cell rather than direct interactions between PGCs. This raises questions about what parameters make one migratory cell more fit than another and whether fitness at this stage of germ cell development translates into the production of better gametes in adulthood.

One proposed parameter of fitness is PGC speed or efficiency of migration. As we have shown, PGCs are found in multiple locations at a single time point, with each location differentially influencing the rate of PGC proliferation (Cantú *et al.*, 2016). Thus, we predict that those leader PGCs first to exit the cell cycle-suppressive environment of the hindgut would gain a head start in proliferation over cells that exit later in development. Due to the dramatic morphological growth that occurs in tissues along the migratory route, early migrators, dubbed 'pioneers', are expected to more rapidly traverse the different somatic compartments to reach the gonads because these tissues are smaller and in closer proximity (Gomperts *et al.*, 1994; Molyneaux *et al.*, 2001). Thus, the proposed distance of travel for leading PGCs is predicted to be shorter than that of PGCs who initiate migration later in development. The consequence of this increased migratory efficiency is that a greater

number of leading PGC progeny would be found in the gonadal ridges and likewise dominate the germ cell pool. However, the basis for differences in migratory capacity of PGCs remains unclear; do the lead migrants exhibit a greater capacity for movement, are they stochastically designated, or do they reflect the first PGCs specified? Migratory capacity may also function deterministically in the distribution of PGCs within the gonadal ridges and subsequently influence their progression through later stages of germ cell development, such as meiotic entry.

One hypothesis put forth nearly 50 years ago is that PGCs which enter meiosis first are the first to mature into follicles and be ovulated, also known as the "production line" hypothesis (Henderson and Edwards 1968). In the mouse, meiotic initiation occurs in a wave starting from the anterior end of the ovary and moving to the posterior (Menke *et al.,* 2003), so location within the tissue dictates order of meiosis, which may be linked to timing of follicle formation and ovulation in adulthood (Zheng *et al.,* 2014). How PGCs are distributed in the gonads during and following migration is unknown, although it is likely a mix of active and passive processes (Clark and Eddy 1975; Anderson *et al.,* 2000). Thus far, live imaging has not revealed a clear bias for the first PGC migrators out of the hindgut to exit from a particular region along the anterior-posterior axis (Gomperts *et al.,* 1994; Molyneaux *et al.,* 2001), although this has not been rigorously examined. In systemic *Ror2* loss-of-function mutants, we observed a semipenetrant defect in which PGCs are unable to colonize the tip of the gonad (Laird *et al.,* 2011; Arora *et al.,* 2016). This likely arises from a combination of defects in axis elongation, due to the function of *Ror2* in mesoderm and somites (Takeuchi *et al.,* 2000; Oishi *et al.,* 2003), and reduced efficiency of migration due to the cell autonomous function of *Ror2* in PGCs. Why PGCs in some of these animals fail to fill the gonadal ridge evenly remains a mystery; however, this defect does not produce a delay in meiotic entry when we controlled for changes in ovary size or position on the anteroposterior axis (Arora *et al.,* 2016). Because *Ror2*-mutant embryos do not survive beyond birth (Takeuchi *et al.,* 2000; DeChiara *et al.,* 2000; Oishi *et al.,* 2003), we have been unable to use these animals to test the link between migration, meiosis, and ovulation. Thus, we expect genetic lineage tracing approaches will provide the best means to track the fate of leader versus laggard PGCs.

Such approaches are not limited to testing the "production line" hypothesis and folliculogenesis, but could also be applied to the study of male germline development. The relationship between migratory fitness and survival during the apoptotic wave in later fetal development or clonal dominance in adult spermatogonial stem cells would be obvious questions to address (Coucouvanis *et al.,* 1993; Goriely and Wilkie 2012).

5 Conclusions

There is much to be learned about the pilgrimage of PGCs to the temple of the gonad, with respect to the fundamental mechanisms as well as the potential function. Here we propose that the process of migration acts selectively to cull cells with insufficient ability to respond to chemotactic cues, metabolic deficiency, and conversely to favor the expansion and priority of meiotic initiation of those who migrate earlier, farther, or faster. The basis of such differences may lie in the number of genetic mutations or differences in epigenetic

reprogramming. If our hypothesis is correct, then it will have implications for understanding of extragonadal germ cell tumors such as SCTs, which may result from failed quality control. Furthermore, it may be important to consider the role of PGC migration in the context of *in vitro* gametogenesis. The emerging possibility of growing eggs from pluripotent cells in a dish recapitulates much of development, but bypasses the process of migration (Hikabe *et al.*, 2016). Would challenging *in vitro* derived PGCs to migrate increase the quality of the gametes obtained, as measured by the frequency of fertilizable eggs and embryo development?

Acknowledgments

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Highlights

- Mechanisms of PGC migration vary by organism, though the process is highly conserved

- Migratory PGCs may gain a proliferative edge by being first to reach pro-mitotic soma

- Cell competition during migration may select PGCs based on relative fitness

- Extragonadal germ cell tumors may arise from heterogeneous PGC migration and survival
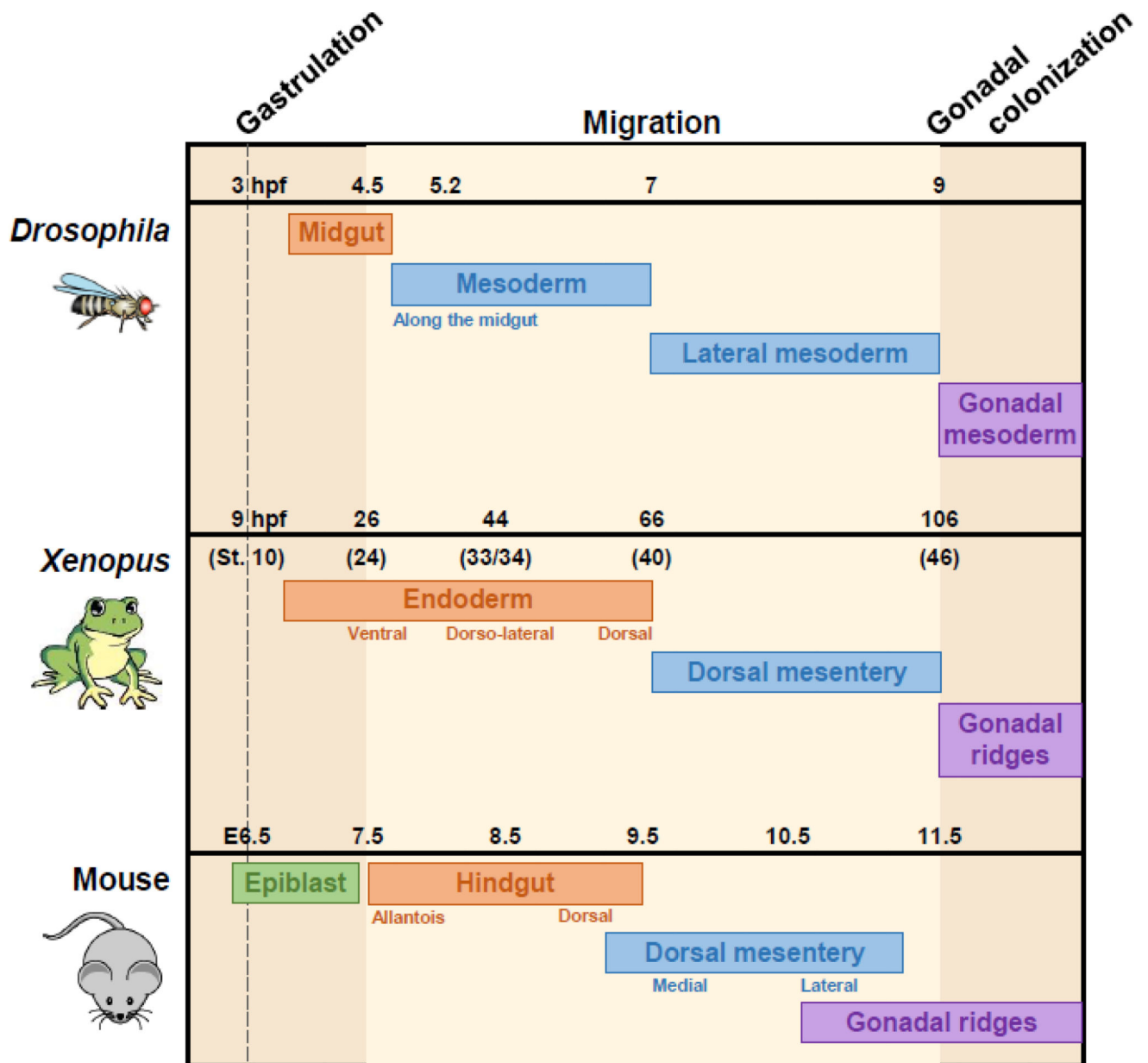
Figure 1. Conservation of PGC migration between multiple species
Following gastrulation (dashed line), PGCs in *Drosophila, Xenopus*, and mouse undergo lengthy migrations through endodermal sheets (orange) and mesodermal tissues (blue) to reach the developing gonads (purple). Time scales of the migratory period are noted for each species; hpf = hours post-fertilization, E = embryonic day. Light beige background denotes the migratory period; darker beige background represents pre- and post-migratory periods. Annotations underneath each bar represent specific locations and timing of PGC movement within the more general tissue type.