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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 additional 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.

1. Introduction

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 (Charleux, 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 and Collodi, 2013).

The study of PGC development in flies, fish, birds, amphibians and mammals reveals surprising diversity in 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* (Fig. 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 (Fig. 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

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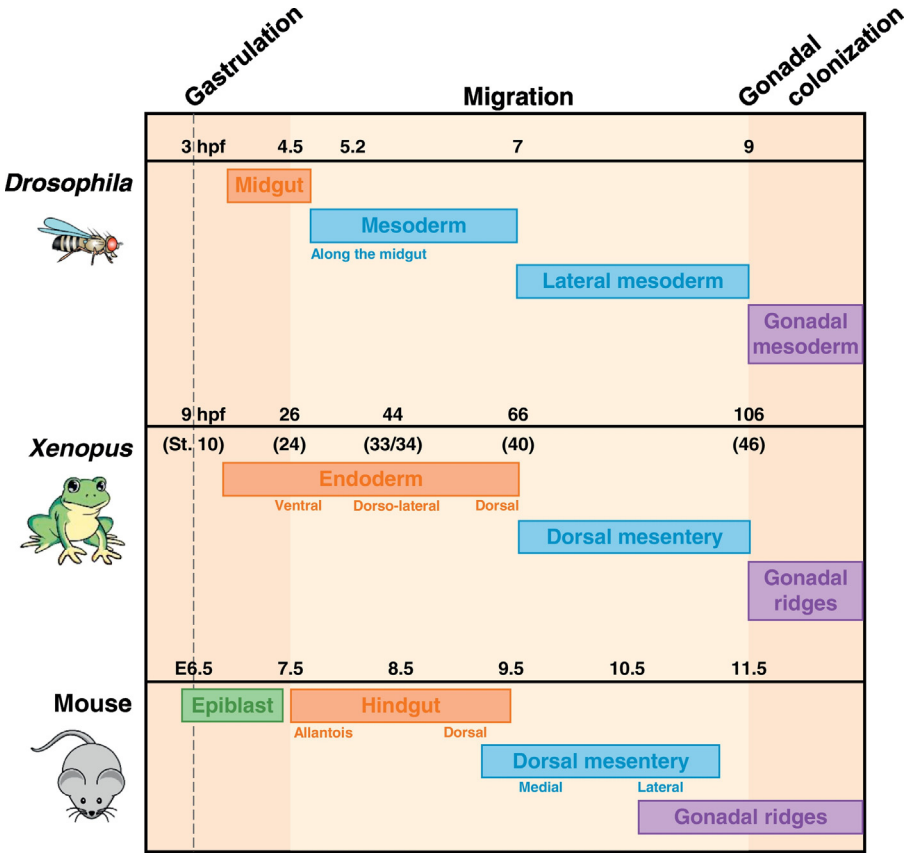

Fig. 1. Conservation of PGC migration between multiple species. Following gastrulation (dashed line), PGCs in *Drosophila*, *Xenopus*, and mouse undergo lengthy migrations through endodermal sheets (orange) and mesodermal tissues (blue) to reach the developing gonads (purple). Time scales of the migratory 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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.

2. The yin and yang of mouse PGC migration

Mouse PGCs begin their migration in the epiblast at E7.5, traverse the primitive streak and allantois to the hindgut endoderm, travel within the growing hindgut epithelium, then egress through the mesentery before colonizing the emerging gonads by E11.5 (Fig. 1; Anderson et al., 2000). 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).

2.1. 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 Ewen 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, 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 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

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