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Receptor tyrosine kinase signaling and primordial germ cell development

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Abstract

Germ cells of an animal are a distinct cell population set aside to ensure transmission of genetic information from one generation to the next. These cells are in a sense immortal as the germ cell lineage is passed from generation to generation, raising questions of how they are maintained and their development controlled. During animal development, primordial germ cells (PGCs) are specified early during embryogenesis either by maternally inherited cytoplasmic determinants or by inductive events via cell-cell interactions. PGCs are usually morphologically distinct from the somatic cells and are more motile, as they have to travel from their place of origin along and through other tissues to eventually colonize in the site of the gonad (reviewed by refs. 1–4) Interestingly, in spite of their uniqueness, PGCs share certain behavioral properties with metastasizing cancer cells. Both types of cells are able to proliferate, invade other tissues, survive in the new environment, and aggregate to form a tissue mass. Thus *Drosophila* primordial germ cells provide an excellent model system to genetically dissect the mechanisms underlying the complex behavioral patterns of cell migration.

Keywords

Drosophila; JAK; STAT; Ras; Torso; receptor tyrosine kinase (RTK); primordial germ cells

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Recently, we found that the *Drosophila* receptor tyrosine kinase Torso (Tor) activates both STAT and Ras during the early phase of PGC development – proliferation and cell shape changes. In later embryogenesis, STAT and Ras activation appear to be required continuously for PGC invasion, survival, and directed migration.[5] We demonstrated that embryos mutant for *stat92E* or *Ras1* have fewer PGCs, and these cells migrate slowly, errantly, and fail to coalesce. Conversely, overactivation of these molecules causes supernumerary PGCs, their premature transit through the gut epithelium and ectopic colonization.[5] A requirement for RTK in *Drosophila* PGC development is analogous to the mouse, in which the RTK c-kit is required, suggesting a conserved molecular mechanism governing PGC behavior in flies and mammals. Furthermore, the finding that STAT and Ras/Raf coactivation is essential for multiple aspects of PGC behavior suggests that primordial germ cells and cancer cells utilize common intrinsic signaling strategies to control their behaviors.

The Tor RTK has been known for its requirement in patterning *Drosophila* embryonic anterior and posterior terminal structures (reviewed by ref 6). Since the Tor protein is present only transiently in early embryos,[7–9] its requirement in patterning terminal structures has been proposed to be the sole function of Tor during *Drosophila* development. Therefore our finding that Tor is involved in germ cell migration was initially unexpected. However, there is a precedent for the requirement of an RTK in germ cell migration in the mouse.

Mutations in the mouse genes *dominant white-spotting* (*W*)[10] and *Steel* (*Sl*)[11,12] cause migration and proliferation defects in germ cells as well as a few other cell types (reviewed by ref. 13). W encodes the proto-oncoprotein c-kit, an RTK that is expressed on the membrane of mouse PGCs. Sl encodes the c-kit ligand termed stem cell factor (SCF), which is localized on the membrane of somatic cells associated with PGC migratory pathways. Interestingly, c-kit and Tor share structural similarities and both are structurally similar to the platelet derived growth factor (PDGF) receptor, in which an insert region separates the intracellular kinase domain. Moreover, similar to Tor and the PDGF receptor, c-kit is able to activate STAT molecules[14–16] as well as the Ras-MAPK cascade.[17] Although true molecular homologs of c-kit and SCF were not yet found in *Drosophila* genome, the functional and structural similarities between Tor and c-kit suggest that flies and mice share molecular mechanisms for regulating primordial germ cell proliferation and migration.

Although we have shown that Ras and STAT activation are likely required continuously for PGC migration, Tor is unlikely the RTK that is responsible for activating these intracellular signaling pathways, as Tor is not expressed in late stages of embryogenesis. It is not clear whether another RTK or separate receptors function to activate Ras and STAT signaling during late PGC migration. The mechanisms of guiding PGC migration are likely complicated and may not be conserved among organisms. For instance, several genes have been identified in *Drosophila* that act in somatic cells to influence the migration of PGCs. These genes include *wunen*, encoding the lipid phosphate phsphtatase-1 homolog, and *columbus*, encoding a HMG-CoA reductase.[18,19] The products of these genes are involved in lipid metabolism and are thought to be responsible for the production of spatial cues that guide PGC migration. In addition, it has recently been shown that Hedgehog (Hh), secreted from the somatic gonadal precursor cells, can serve as an attractive guidance cue for the migrating PGCs.[20] Recently, the chemokine SDF1 and its receptor Cxcr4, a G-protien coupled seven-transmembrane protein, were identified in genetic screens as required for guiding Zebrafish PGC migration.[21,22] The orthologs for many of the molecules identified in particular genetic model organisms have not been identified or found functionally conserved across species. Thus it is possible that multiple signaling mechanisms act in concert to ensure the migrating PGCs to reach the correct target tissue. Our results from misexpressing the fly JAK/STAT ligand Unpaird (Upd) are consistent with a hypothesis that PGCs follow spatial cues provided by somatic tissues that secret ligands triggering STAT92E and/or Ras1/Draf activation, and disruption of the guidance cues, such as by misexpressing the ligand Upd, would alter the path of PGC migration.[5]

PGCs are not the only cell type that is capable of migration during normal development. Indeed, the ovarian border cells of *Drosophila* are also capable of invasive and guided migration. Border cells of the *Drosophila* ovary are follicle cells that, during oogenesis, delaminate as a cluster 6–10 cells from the anterior follicle epithelium, invade the nurse cells, and migrate toward the oocyte. Interestingly, it has been shown that the detachment and guided migration of these cells require STAT92E activation.[23–25] Mutations in components of the Hop/STAT92E pathway cause border cell migration defects.[23,24] On the other hand, border cell migration also requires RTK signaling.[26] An RTK related to mammalian PDGF and VEGF receptors, PVR, is required in border cells for their guided migration toward the oocyte. PVR appears functionally redundant with another fly RTK, EGFR, in guiding border cells.[26] Taken together, these results indicate that the invasive behavior and guided migration of *Drosophila* ovarian border cells require both STAT92E and RTK activation. In light of our results from analyzing PGC migration, we propose that activation of both STAT and components downstream of RTK signaling may serve as a general mechanism for invasive and guided cell migration.

Why PGCs require activating the Ras and STAT pathways for their development? Although PGCs express a unique repertoire of genes that differentiate themselves from somatic cells, it is obviously mostly economical during evolution that they utilize existing cellular strategies to control their movement. It has been shown that actin-based cytoskeletal reorganization plays a crucial role in cell shape changes and movements. The identification of STAT and Ras coactivation as an essential requirement for PGC migration raised an interesting question of how STAT and Ras signaling pathways coordinate the cytoskeletal reorganization required for PGC migration. STAT92E has been shown to be involved in the transcriptional activation of many signaling molecules as well as key transcription factors.[23,27–29] A recent systematic search for STAT92E target genes have revealed a plethora of genes that might be directly activated by STAT92E, among which are those involved in the regulation of cytoskeletal movements and actin reorganization (F. Xia and W. X. Li, unpubl. data). Upregulation of such genes in response to spatial cues should facilitate cell movements. Moreover, in a separate line of research, we examined the tissue-specific localization of the tyrosine-phosphorylated, or activated form of STAT92E and found that during *Drosophila* embryonic development STAT92E is active in tissues undergoing morphogenetic movements, such as the invaginating tracheal pits, elongating intestinal tracks, and growing axons.[30] We further demonstrated that *stat92E* mutants are defective in tracheal development, hindgut elongation, and axonal growth. Conversely, STAT92E overactivation caused premature development of the tracheal and nervous systems, and over-elongation of the hindgut.[30] These results suggest that STAT activation might be generally involved in morphogenetic movements during metazoan development. On the other hand, Ras and other small GTP proteins have been implicated in multiple cellular processes that require cytoskeletal reorganization. It remains to be determined how these two signaling pathways coordinate primordial germ cell movements in response to guidance cues from surrounding somatic tissues and which genes in PGCs require input from both the Ras and STAT pathways for their expression.

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