Receptor Tyrosine Kinases in *Drosophila* Development

Richelle Sopko[1] and Norbert Perrimon[1,2]

[1]Department of Genetics, Howard Hughes Medical, Institute Harvard Medical School, Boston, Massachusetts 02115

[2]Howard Hughes Medical, Institute Harvard Medical School, Massachusetts 02115

Correspondence: perrimon@receptor.med.harvard.edu

Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

Tyrosine phosphorylation plays a significant role in a wide range of cellular processes. The *Drosophila* genome encodes more than 20 receptor tyrosine kinases and extensive studies in the past 20 years have illustrated their diverse roles and complex signaling mechanisms. Although some receptor tyrosine kinases have highly specific functions, others strikingly are used in rather ubiquitous manners. Receptor tyrosine kinases regulate a broad expanse of processes, ranging from cell survival and proliferation to differentiation and patterning. Remarkably, different receptor tyrosine kinases share many of the same effectors and their hierarchical organization is retained in disparate biological contexts. In this comprehensive review, we summarize what is known regarding each receptor tyrosine kinase during *Drosophila* development. Astonishingly, very little is known for approximately half of all *Drosophila* receptor tyrosine kinases.

One of the key strategies that arose during evolution to facilitate the transmission of extracellular information was that of receptor tyrosine kinase (RTK) signaling. This mechanism enables cells to transduce cues from their extracellular environment and thus contributes extensively to developmental processes. Today, we have come to recognize conserved RTK signaling as crucial for most aspects of cell fate determination, differentiation, patterning, proliferation, growth, and survival in metazoans. Activation of RTKs by ligand leads to a canonical deployment of signal transduction involving adaptor proteins, serine/threonine kinases, and transcription factors essential for animal development.

RTKs function reiteratively in different contexts during development to direct, restrain, or alter the commitment of a cell. Genetically tractable model organisms such as *Drosophila melanogaster* have proven instrumental in deciphering the roles of RTKs during development as well as their signaling pathways. Furthermore, extension of this knowledge to mammalian orthologs has substantially broadened our understanding of the function of RTKs in development and cellular transformation. Approximately 20 RTKs are encoded by the *Drosophila* genome, nearly all of which have a mammalian counterpart (Table 1). In this article, we review what we know to date about their functions, illustrating the diversity of cellular

Editors: Joseph Schlessinger and Mark A. Lemmon
Additional Perspectives on Signaling by Receptor Tyrosine Kinases available at www.cshperspectives.org

 doi: 10.1101/cshperspect.a009050
Cite this article as *Cold Spring Harb Perspect Biol* 2013;5:a009050

Table 1. Drosophila RTKs/ligands/signaling components/transcription factors

Flybase ID	Symbol	Name	Mammalian homolog	Ligand	Characterized signaling pathway components
FBgn0040505	Alk	Alk	ALK	Jelly belly	mtg, Ras1, rl
FBgn0053531	Ddr	Discoidin domain receptor	DDR1 and DDR2	Collagen?	
FBgn0024245	dnt	Doughnut on 2	RYK	Wnt5?	
FBgn0015380	drl	Derailed	RYK	Wnt5	Src64B
FBgn0033791	Drl-2	Derailed 2	RYK	Wnt5	
FBgn0003731	Egfr	Epidermal growth factor receptor	EGFR	Spitz, Gurken, Vein, Keren	rho, Star, Ras1, Sos, csw, phl, Shc,dos, Gap1, Dsor, drk, ksr, cnk, rl, pnt, aop, ttk, sprouty, kekkon, argos
FBgn0025936	Eph/Dek	Eph receptor tyrosine kinase	EPHA and EPHB	Ephrin, Vap33, Exn	kuz, Exn, cac, Cdc42
FBgn0010389	htl/DFR1/ Dtk1	Heartless	FGFR	Pyramus, Thisbe	Ras1, stumps, csw, rl, aop, pnt
FBgn0005592	btl/DFR2/ Dtk2	Breathless	FGFR	Branchless	Ras1, stumps, csw, drk, Shc, Sos, ksr, cnk, sprouty, rl, grh, gro, pnt, aop
FBgn0013984	InR	Insulin-like receptor	INSR/IGF1R	Ilp1-7	chico, Sos, Drk, Shc, Ras, Pten, Pi3K92E, Pi3K21B, Pdk1, Tsc1, gigas, Rheb, Tor, Akt1, S6k, foxo
FBgn0038279	CG3837		INSR/IGF1R	Ilps?	
FBgn0032752	CG10702		INSR/IGF1R	Ilps?	
FBgn0032006	Pvr	PDGF- and VEGF-receptor related	VEGFR and PDGFR	PVF1,2,3	Ras1, rl, aop, Rac, mbc, ELMO, Crk, Cdc42
FBgn0011829	Ret	Ret oncogene	RET		
FBgn0010407	Ror	One of two Ror kinases	Ror1 and Ror2	Orphan receptor	
FBgn0020391	Nrk	Neurotropic receptor kinase	MuSK	Orphan receptor	
FBgn0004839	otk/Dtrk	Offtrack	Trk	Wnt4	plexA, dsh
FBgn0003366	sev	Sevenless		Boss	Ras1, Sos, csw, phl, drk, dos, ksr, Gap1, Dsor, rl, aop, Pnt, Lz
FBgn0003733	tor	Torso		Trunk	Torso-like, fs(1)N, fs(1)ph, Ras1, Sos, csw, Shc, dos, Gap1, ksr, phl, Dsor, drk, rl, cic, gro
FBgn0022800	Cad96Ca/ Stitcher	Cad96Ca			rl, grh
FBgn0014073	Tie	Tie-like receptor tyrosine kinase			

processes controlled by RTK signaling as well as the extent of pleiotropy associated with specific RTKs.

Torso: AN RTK DETERMINANT OF ANTERIOR/POSTERIOR PATTERNING AND METAMORPHOSIS

The first RTK to be deployed during *Drosophila* embryogenesis is Torso. Torso is maternally contributed and localized uniformly to the membrane of the syncytial blastocyst. Localized activation of Torso involves the processing of its presumptive ligand, Trunk, at the egg poles, a process requiring at least three genes: *torso-like*, *fs(1)Nasrat (fs(1)N)*, and *fs(1)polehole (fs(1)ph)* (Casanova and Struhl 1989; Sprenger et al. 1989; Stevens et al. 1990; Perrimon et al. 1995; Casali and Casanova 2001). Progeny derived from females lacking *torso*, *trunk,* or any of the aforementioned "terminal class genes" fail to develop stereotypical head and tail structures (Perrimon et al. 1986; Schupbach and Wieschaus 1986; Nüsslein-Volhard et al. 1987). Gain-of-function alleles of *torso*, on the other hand, drive the opposite phenotype: embryos with an extended posterior domain and minimal thoracic and abdominal regions (Klingler et al. 1988; Casanova and Struhl 1989; Schupbach and Wieschaus 1989; Strecker et al. 1989; Szabad et al. 1989). Screens to uncover suppressors of a *torso* gain-of-function allele identified *Ras1* and *son of sevenless* (*Sos*). Further epistasis experiments positioned *corkscrew* (*csw*; *SHP2*), *SHC-adaptor protein* (*Shc*), *GTPase-activating protein 1* (*Gap1*), *kinase suppressor of ras* (*ksr*), *leonardo* (*leo*; *14-3-3ζ*), *polehole* (*phl*; *RAF*), *Downstream of raf1* (*Dsor; MEK*), *downstream of receptor kinases* (*drk; GRB2*), and *rolled* (*rl*; ERK) within the hierarchy responsible for transducing the downstream signal from Torso (Ambrosio et al. 1989a,b; Casanova and Struhl 1989; Stevens et al. 1990; Perkins et al. 1992; Doyle and Bishop 1993; Lu et al. 1993, 1994; Tsuda et al. 1993; Brunner et al. 1994; Hou et al. 1995; Therrien et al. 1995; Li et al. 1997; Luschnig et al. 2000) (Fig. 1).

Torso activation peaks between 1–2 hr of embryonic development (Sprenger and Nüsslein-Volhard 1992; Sprenger et al. 1993) results in the expression of *tailless* (*tll*) and *huckebein* (*hkb*), genes encoding for transcriptional repressors, at the embryonic poles (Moran and Jimenez 2006). These "terminal gap genes" demarcate zones of differentiation and embryos deficient for these gene products display phenotypes resembling those deficient for other members of the maternal terminal class (Pignoni et al. 1990; Weigel et al. 1990; Brönner and Jäckle 1991). The terminal class gene, *rl/ERK*, is upstream of *tll*, based on the fact that gain-of-function mutations in *rl/ERK* are unable to rescue *tll* null mutant embryos (Brunner et al. 1994). Phosphorylation of the transcriptional repressor Capicua (Cic) and corepressor Groucho (Gro) by activated ERK relieves transcriptional

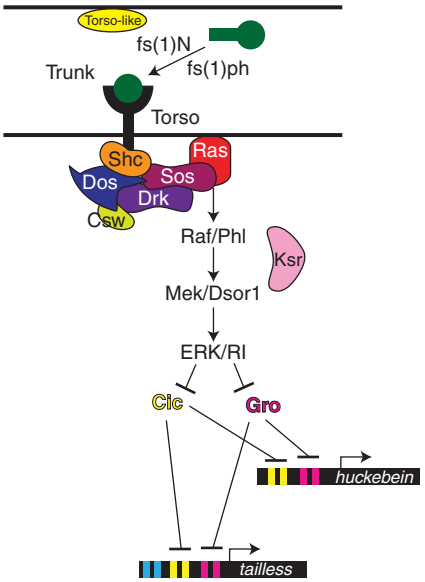

Figure 1. Torso activation in embryogenesis. Processing of the Torso ligand Trunk occurs locally at the anterior and posterior embryonic poles and requires Torso-like, fs(1)N, and fs(1)ph. Engagement of Torso by processed Trunk triggers Torso autophosphorylation and subsequent recruitment of downstream adaptors and effectors. A phosphorylation cascade initiated by Tor activation and involving Raf/Phl, Mek/Dsor1, and ERK/Rl leads to the inhibition of transcriptional repression by Cic and Gro. This permits gap gene (*tailless* and *huckebein*) and subsequent pair-rule gene expression and enables patterning of the developing embryo.

repression of *tll* and *hkb* at the embryonic posterior pole (Astigarraga et al. 2007; Cinnamon et al. 2008; Helman et al. 2011). At the anterior pole, Torso activation down-regulates the homeodomain transcription factor Bicoid by phosphorylation-independent mechanisms, in addition to inactivating Cic and Gro (Pignoni et al. 1992; Ronchi et al. 1993; Bellaïche et al. 1996; Janody et al. 2001). At both termini, Torso signaling inhibits Gro and permits Tll-dependent suppression of gap gene expression, whereas active Gro in central regions is unaffected and can repress *tll* expression, permitting central gap gene expression and in this way establishing expression "stripes" (Steingrímsson et al. 1991; Moran and Jimenez 2006). Gap genes encode for transcription factors that will activate expression of pair-rule genes. This sequential activation of gene expression enables patterning of the developing embryo (Nasiadka et al. 2002).

Torso also functions as a receptor for the neuropeptide prothoracicotropic hormone (PTTH) in the *Drosophila* brain during metamorphosis (Rewitz et al. 2009). Torso engagement by PTTH in the prothoracic gland (PG), an endocrine organ in insects, triggers Ras/Raf/ERK signaling to drive the production and/or release of the hormone ecdysone. Reduction of *torso* by RNAi specifically in the PG results in developmental delays similar to that resulting from ablation of PTTH-expressing neurons (McBrayer et al. 2007). PTTH shares significant structural homology with the Torso ligand Trunk and can substitute for Trunk in terminal signaling during embryogenesis (Rewitz et al. 2009).

Sevenless: AN RTK SPECIFYING CELL FATE IN THE *Drosophila* EYE AND TESTES

The *Drosophila* compound eye is comprised of 750–800 repetitive units termed ommatidia. Each ommatidium consists of eight photoreceptor neurons (R1–R8) and four lens-secreting cone cells, surrounded by a net of pigment cells that optically insulate each ommatidium from its neighbors (Wolff and Ready 1993). The spectral specificity of photoreceptor subtypes is provided by G-coupled Rhodopsin receptors. Photoreceptor differentiation occurs during the larval stage wherein a progressive "wave" of cell differentiation proceeds from the posterior to anterior region of the eye imaginal disc, the precursor of the adult eye. This wave (the morphogenetic furrow; MF) is visualized as a narrow indentation of epithelial cells contracting in the apical-basal dimension in a concerted fashion. Posterior to the MF, differentiated cells arrange into clusters and adopt the mature ommatidium pattern (Voas and Rebay 2003). A number of signaling pathways initiate MF progression and cell differentiation including epidermal growth factor receptor (EGFR), Notch, Wingless (Wg), Hedgehog (Hh), JAK-STAT, Decapentaplegic (Dpp), and Sevenless (Sev) (Charlton-Perkins et al. 2011).

R7 is the last photoreceptor to be recruited to the ommatidial cluster and specified. Differentiation of R7 relies on signals from neighboring cells within each ommatidial cluster; engagement of the RTK Sev on the surface of R7 by its membrane-associated ligand Bride-of-Sevenless (Boss), expressed exclusively in R8, triggers Ras/Raf/ERK signaling in R7 (Hart et al. 1990; Krämer et al. 1991; Simon et al. 1991). A lack of Sev activity in the R7 precursor (Tomlinson and Ready 1986, 1987; Tomlinson et al. 1987; Basler and Hafen 1988), or a lack of Boss in R8 (Reinke and Zipursky 1988), redirects R7 cell fate to that of a cone cell. Conversely, a cone cell precursor can be directed to become a R7 photoreceptor if the precursor expresses constitutively active Sev (Basler et al. 1991; Dickson et al. 1992; Sprenger and Nüsslein-Volhard 1992). Normally, the activation of Sev in photoreceptors other than R7, is restricted by the activity of *Socs36E*, expressed in all photoreceptors except R7 (Almudi et al. 2009, 2010), and reinforced in R7 by the adaptor protein Drk, specifically expressed in R7 (Olivier et al. 1993; Simon et al. 1993) (Fig. 2). Ras/Raf/Mek downstream from Sev (and EGFR—see below) results in the phosphorylation by Rl/ERK of two transcription factors critical for photoreceptor specification: Anterior open (Aop) and Pointed-P2 (Pnt-P2). Phosphorylation inhibits the repressor activity of Aop (O'Neill et al. 1994) by targeting it for nuclear export (Tootle et al. 2003) and degradation

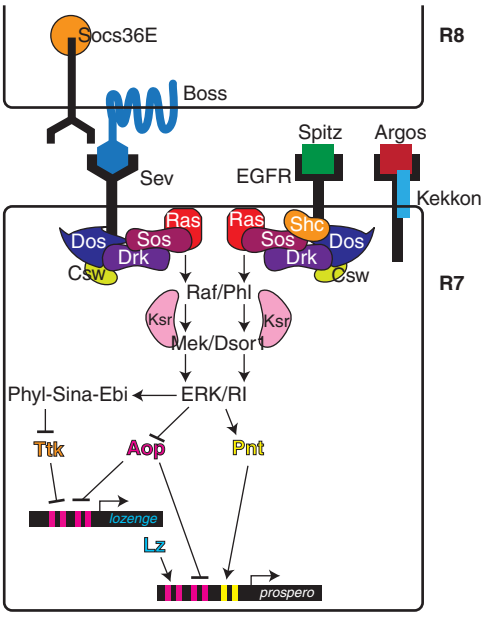

Figure 2. Sevenless and EGFR signaling in photoreceptor specification. Engagement of Sev on the R7 photoreceptor cell by its ligand Boss on R8 activates the Ras/Raf/Mek/ERK signaling cascade in R7. A similar cassette of signaling proteins execute EGFR-dependent functions, following EGFR activation by its ligand Spitz. Sev activation in R8 is prevented by Socs36E and reinforced in R7 by the adaptor protein Drk, whereas Argos and Kekkon limit EGFR activation. Phosphorylated and active ERK/Rl targets the transcriptional repressors Aop and Ttk (via Phyl-Sina-Ebi) for degradation, whereas ERK-dependent phosphorylation stimulates Pnt transcriptional activity. This relieves transcriptional repression at *lozenge* and *prospero* enhancers. Lz functions together with Pnt to activate *pros* expression, thus providing R7 identity by repressing the expression of cone cell and R8-specific rhodopsins.

(Rebay and Rubin 1995). Pnt-P2, on the other hand, requires phosphorylation for its activity (Brunner et al. 1994; O'Neill et al. 1994). These factors play antagonistic roles in regulating the *lozenge* (*lz*) enhancer directly (Xu et al. 2000; Behan et al. 2002; Jackson Behan et al. 2005). High levels of RTK signaling in the prospective R7 cell relieve Tramtrack (Ttk)-dependent repression of *lz* (Daga et al. 1996; Xu et al. 2000; Siddall et al. 2009). Rl/ERK targets Ttk to the E3 ubiquitin ligase complex (comprised of Seven in absentia, Ebi, and Phyllopod) for degradation (Lai et al. 1997, 2002; Tang et al. 1997; Boulton et al. 2000; Li et al. 2002). Lz regulates *prospero* (*pros*) expression specifically in R7 by binding the *pros* enhancer directly. Lz works with Pnt-P2 at the *pros* enhancer, when Aop is displaced because of high ERK activity (Xu et al. 2000; Jackson Behan et al. 2005; Hayashi et al. 2008; Siddall et al. 2009). Pros functions to repress the expression of cone cell and R8-specific Rhodopsins thereby providing identity to R7 (Cook et al. 2003).

Genetic screening for modifiers of *sev* phenotypes identified many players downstream from Sev, including Ras1, Sos, Raf, Drk/Grb2, Dos, Csw, Gap1, and Rl/ERK (Rogge et al. 1991, 1992; Simon et al. 1991; Dickson et al. 1992; Gaul et al. 1992; Olivier et al. 1993; Biggs et al. 1994; Brunner et al. 1994; Raabe et al. 1996). These experiments were among the first to identify the genetic requirements for RTK signaling and in doing so delineate the hierarchy of canonical RTK signaling.

As is the case of Torso, Sev has also been shown to play a role in an additional cell type, in this case the male testes. Sev is required in a subset of somatic cells of the male embryonic gonad to spatially restrict stem cell niche differentiation. Sev activation in posterior somatic gonadal cells by Boss, presented by adjacent primordial germ cells, represses their differentiation into hub/niche cells and thereby restricts germline stem cell numbers (Kitadate et al. 2007).

EGFR: AN RTK WITH MULTITUDE ROLES

The *Drosophila* EGFR is involved in numerous developmental decisions throughout the *Drosophila* life cycle. For instance, the EGFR pathway has roles in dorsal/ventral patterning of the embryonic ectoderm and the establishment of neuroectoderm, wing development, antennal formation, photoreceptor differentiation, lamina neuron differentiation, and the specification of muscle precursors and invagination of tracheal branches to name a few (Perrimon and Perkins 1997; Shilo 2003). EGFR predominantly mediates short-range signaling that is restricted

either to the cells producing EGF or to cells positioned 1–2 cells away. EGFR activates the canonical Ras/Raf/MEK/ERK pathway and visualization of pathway activity has documented the highly dynamic activity of EGFR signaling (Gabay et al. 1997) (Fig. 2). Multiple EGFR ligands and feedback loops are responsible for the complex temporal and spatial regulation of EGFR signaling (Perrimon and McMahon 1999; Shilo 2005). Regarding activation, there are four EGFR ligands in *Drosophila*: Spitz, Keren, Gurken, and Vein, with Vein being the only secreted protein that does not require processing for its activity. Detailed studies of ligand processing, in particular of Spitz, have shown a requirement for two proteins, Star and Rhomboid (Rho). Star is a type II transmembrane protein that associates with Spitz, facilitating its translocation from the ER to a cellular compartment where it is cleaved by the seven-pass transmembrane protein Rhomboid (Rho). Importantly, although Star expression is ubiquitous, Rho is extremely dynamic and thus responsible for controlling EGFR activation in a wide range of tissues. Finally, the transcriptional induction of negative regulators of the pathway restricts the spatial and temporal activation of EGFR signaling. These include the cytoplasmic proteins Sprouty and Cbl, the extracellular secreted molecule Argos, and the extracellular transmembrane protein Kekkon. A comprehensive description of the entirety of EGFR function during *Drosophila* development would exhaust the page limitations of this chapter and so we refer readers to a comprehensive review (Shilo 2005).

FGFR SUPERFAMILY: HEARTLESS AND BREATHLESS

Heartless: An RTK Influencing Mesodermal Cell Migration and Cell Specification

The gene product encoded by *heartless* (*htl*) shares ~60% identity in its kinase domain with vertebrate FGFRs and 80% identity with the other FGFR homolog in *Drosophila*, Breathless (Btl). *htl* is expressed ~2.5 hr postfertilization in presumptive mesoderm at the onset of gastrulation. *htl* expression persists throughout embryogenesis in somatic muscle precursors including cardiac and pericardial cells, pharyngeal muscle cells, visceral muscle precursors, and additionally in glia of the central nervous system (CNS) (Shishido et al. 1993; Hidalgo and Booth 2000; Egger et al. 2002; Freeman et al. 2003). During larval stages, *htl* is expressed in muscle cell precursors of wing and leg imaginal discs and in neural precursors and glia of the brain and eye imaginal discs (Emori and Saigo 1993; Sato and Kornberg 2002; Butler 2003; Butler et al. 2003; Franzdóttir et al. 2009). During pupal and adult stages, *htl* is expressed in abdominal and thoracic myoblasts (Dutta et al. 2005).

After ventral furrow invagination, the mesoderm primordium undergoes an epithelial-to-mesenchymal transition and spreads dorsally over ectodermal cells to form a monolayer (Schumacher et al. 2004; Wilson 2005; Wilson et al. 2005; Clark et al. 2011). This repositioning is required for the reception by mesodermal cells of patterning cues (Dpp and Wg) from the adjacent ectoderm that specifies the mesoderm lineage into visceral mesoderm, heart tissue, somatic muscle, and the fat body (FB). *htl* null mutant embryos show defects in the bilateral spreading of mesoderm during gastrulation (Murray and Saint 2007; McMahon et al. 2008). *htl* mutants fail to develop visceral mesoderm and heart tissue, whereas somatic muscles are disorganized and reduced because of the absence of differentiated mesodermal subtypes. *htl* mutants show additional defects: failure of CNS glia to migrate and ensheath longitudinal ventral nerve cord (VNC) connectives, and defective salivary gland migration (Beiman et al. 1996; Gisselbrecht et al. 1996; Shishido et al. 1997; Michelson et al. 1998b; Schulz and Gajewski 1999; Mandal et al. 2004).

Expression of activated Ras1 partially rescues mesodermal defects associated with *htl* perturbation (Beiman et al. 1996; Gisselbrecht et al. 1996; Michelson et al. 1998b; Schulz and Gajewski 1999). Ras1 functions downstream or parallel to the adaptor protein Stumps (Carmena et al. 1998; Michelson et al. 1998a; Vincent et al. 1998; Imam et al. 1999) to transduce signals

downstream from Htl (Johnson Hamlet and Perkins 2001; Petit et al. 2004; Csiszar et al. 2010). Ectopic expression of activated Aop, a transcriptional repressor downstream from ERK, generates phenotypes similar to that due to *htl* disruption whereas expression of activated Pnt, a transcriptional activator downstream from ERK, increases the number of somatic muscle progenitors (Halfon et al. 2000). These observations are consistent with Htl-dependent ERK activation (Gabay et al. 1997; Wilson et al. 2004).

Thisbe (*ths*) and *pyramus* (*pyr*), ligands for Htl, are expressed in the neurogenic ectoderm coincident with the migration of mesoderm during gastrulation. They are later differentially expressed in other epithelial tissues that flank mesodermal derivatives: the stomadeum, the hindgut, the CNS, and at muscle attachment sites. *ths* and *pyr* mutants are defective in mesodermal cell intercalation and monolayer formation after dorsal spreading. ERK activation at the leading edge of the migrating mesoderm is absent in *ths pyr* double mutants, and expanded as a result of ectopic *ths* expression similar to that attributable to constitutively active Htl expression. Constitutively active Htl partially restores mesodermal differentiation to *ths pyr* mutants (Gryzik and Müller 2004; Stathopoulos et al. 2004; Klingseisen et al. 2009; McMahon et al. 2010; Clark et al. 2011).

The anterior migration of caudal visceral mesoderm, giving rise to the longitudinal muscles that ensheath the gut, is guided by Htl activation. *ths* and *pyr*, expressed in adjacent trunk visceral mesoderm, together promote cell survival and restrict lateral movement of caudal visceral mesoderm cells during their migration along trunk visceral mesoderm (Kadam et al. 2012). In the cardiogenic mesoderm, Pyr plays the major role in activating ERK to maintain cardiogenic lineages (Klingseisen et al. 2009; Grigorian et al. 2011). In the eye imaginal disc, *ths* and *pyr* have different expression patterns that translate to unique contributions to Htl signaling: *pyr* for early glia–glia interactions that promote glial cell proliferation and migration, and *ths* for glial–neuron interactions that inhibit migration and trigger cell differentiation (Franzdóttir et al. 2009).

Htl is additionally required in the gonadal mesoderm for primordial germ cell (PMC) migration. In *htl* mutant embryos, PMCs transverse the posterior midgut but stall at the endoderm/lateral mesoderm border. Those few PMCs that infiltrate the lateral mesoderm fail to navigate toward and associate with somatic gonadal precursors (SGPs)—specialized mesodermal cells that give rise to the somatic portion of the gonad. SGPs of *htl* mutant embryos are reduced in number and deranged in shape (Moore et al. 1998).

htl is required in the *Drosophila* ocellar sensory system (OSS), to direct OSS axon development during pupariation. OSS axons migrate toward their targets in the brain, until metamorphosis when they become detached and reorient. Properties such as the ability to attach, detach, or cross to the brain are lost when dominant-negative Htl is expressed in neurons. Genetic evidence implies Htl functions downstream from Neuroglian—a homophilic cell adhesion molecule required for axon guidance—in this context (García-Alonso et al. 2000).

Htl is necessary for larval cardiac tube remodeling, which occurs without cell migration. Htl is additionally required for the formation of ventral imaginal muscle founders and the differentiation of leg imaginal disc associated myoblasts and abdominal/thoracic adult myoblasts. Modulation of Htl activity alters the number of myoblast founder cells and adult muscle fibers (Dutta et al. 2005; Maqbool et al. 2006; Zeitouni et al. 2007).

Breathless: An RTK Influencing Cell Migration and Patterning, Predominantly in the Tracheal System and CNS

Although they share significant identity, the two FGF receptors in *Drosophila*, Breathless (Btl) and Htl differ in their ligand binding domain structure (Shishido et al. 1993). As such, the Htl ligands Pyr and Ths are unable to activate Btl to influence tracheal branching whereas the Btl ligand, Branchless (Bnl), is unable to influence Htl-dependent mesoderm spreading and differentiation (Kadam et al. 2009).

btl is expressed during embryogenesis in the invaginating tracheal primordia and developing tracheal system, the salivary glands, CNS glia and neurons, cells of the gut and male genitalia primordium (Glazer and Shilo 1991; Klambt et al. 1992; Shishido et al. 1993; Ahmad and Baker 2002). *bnl* is expressed in cells surrounding Btl-expressing cells and prefigures their migratory direction (Sutherland et al. 1996).

btl and *bnl* mutant embryos show defects in tracheal cell migration; however, the specification and proliferation of tracheal precursors is normal. The absence of a tracheal system skeleton in *btl* mutants ensues from an inability of cells to coordinately migrate out from the tracheal placodes in stereotyped directions and then intercalate and elongate to form tubes. Further, the formation and fusion of secondary and terminal branches, each derived from a single cell, is compromised in *btl* mutants because of a failure of tracheal cell fate acquisition. Proper tracheal branching relies on the spatial regulation of Btl activity; localized misexpression of *bnl* can redirect tracheal cell migration and induce branching, through the activation of Btl and a downstream Pnt-dependent gene expression program (Klambt et al. 1992; Reichman-Fried and Shilo 1995; Lee et al. 1996; Samakovlis et al. 1996; Sutherland et al. 1996). In this same manner, oxygen deprivation directs fine terminal branching during larval stages—triggering *bnl* expression and therefore, Btl activation—for oxygen delivery (Jarecki et al. 1999; Ghabrial et al. 2011). Branching relies on an extensive number of factors downstream from Btl (Ghabrial et al. 2011). For instance, Btl autophosphorylation, following Bnl binding (Lee et al. 1996; Sutherland et al. 1996), functions to recruit the adaptor protein Stumps. Phosphorylation of Stumps by Btl induces binding of the phosphatase Csw, another component of the signaling cascade that activates ERK (Michelson et al. 1998a; Vincent et al. 1998; Imam et al. 1999; Wilson et al. 2004) (Fig. 3). ERK function is discharged by the transcriptional activator Grh (Hemphala et al. 2003) and the transcriptional corepressor Gro (Cinnamon et al. 2008). ERK-dependent phosphorylation of these factors as well as of the transcription factor Aop, a repressor of *btl*, modulates their activity (Ohshiro et al. 2002). The FGFR inhibitor Sprouty limits the range of Bnl signaling and prevents tracheal branch stalk cells from budding ectopically (Hacohen et al. 1998).

Tracheal branch fusion relies on Btl-dependent *Delta* expression in fusion cells of migrating branches. Delta displayed by the fusion cell activates Notch on adjacent cells to limit fusion cell identity to one cell per branch; Notch down-regulates *bnl* expression to restrict fusion cell identity and delimit ERK activation (Ikeya and Hayashi 1999). Notch-mediated lateral inhibition also restricts the number of leading cells in a branch (Ghabrial and Krasnow 2006). Fusion further depends on a single mesodermal cell—the bridge cell—that guides the

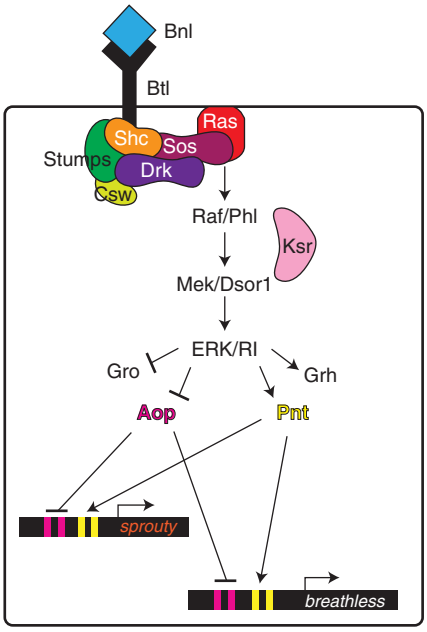

Figure 3. Breathless signaling in the tracheal system. Btl autophosphorylation, on Bnl binding, recruits the adaptor protein Stumps and additional downstream effectors. Ras activation initiates a phosphorylation cascade that culminates in the stimulation of ERK kinase activity. ERK-dependent phosphorylation of the transcriptional activators Grh and Pnt, and the transcriptional repressors Gro and Aop, modulates their activity at promoters. The consequential up-regulation of gene expression induces tracheal cell migration and tracheal branching and fine-tuning of Btl signaling.

extension and fusion of tracheal metameres to generate a continuous dorsal trunk (Wolf and Schuh 2000). Bnl induces filopodial tracheal cell extensions that contact the bridge cell and are essential for dorsal trunk branch fusion (Ribeiro et al. 2002; Wolf et al. 2002).

Btl/Bnl-dependent filopodial extensions are also presented by imaginal tracheoblasts, which proliferate to remodel the adult respiratory system during metamorphosis. The migration of tracheoblasts at the tip of the air sac primordium is dependent on Btl (Sato and Kornberg 2002; Cabernard and Affolter 2005). Btl additionally influences tracheoblast identity in the spiracular branch and the dorsal branch stalk, by inducing tracheoblast differentiation as well as by promoting differentiated cells to reenter the cell cycle, respectively (Guha et al. 2008; Sato et al. 2008; Weaver and Krasnow 2008; Pitsouli and Perrimon 2010).

btl-expressing cells migrate toward distinct populations of *bnl*-expressing cells additionally in the male genital imaginal disc; *bnl* expression by ectodermally-derived genital precursor cells induces *btl*-expressing cell migration into the male disc. The *btl*-expressing mesodermal cells are subsequently converted into epithelia during pupal stages to generate the vascular paragonia and vas deferens. In female genital discs, *bnl* expression is targeted by the female-specific repressor form of the transcription factor Doublesex (Ahmad and Baker 2002).

In the embryonic CNS of *btl* mutants, posterior midline glial cells migrate inappropriately, resulting in irregular commissural patterning (Klambt et al. 1992). Notably, perturbation of *pnt* and *stumps* also generates glial cell migration phenotypes (Klambt 1993; Vincent et al. 1998; Imam et al. 1999). During larval stages of eye patterning Bnl is required for cell adhesion and Hh-dependent apical constriction that enables ommatidial cluster formation. Btl is further required cell autonomously for retinal architectural integrity and noncell-autonomously in directing retinal glia migration (Mukherjee et al. 2012). In the adult brain, Btl is required to mediate axonal retraction rather than guidance specifically in the dorsal cluster neurons (DCN) of the visual system. In this context, Btl is activated in extending DCN axons as they encounter Bnl. Btl signaling activates Rac that in turn inhibits JNK signaling, inducing axonal retraction (Srahna et al. 2006).

INSULIN RECEPTOR RTK SUPERFAMILY: THE INSULIN RECEPTOR AND ANAPLASTIC LYMPHOMA KINASE

The Insulin and Insulin-Like Growth Factor Receptor in *Drosophila*: An RTK Essential for Growth

The insulin-like growth factor receptor in *Drosophila*, *InR*, is ubiquitously expressed throughout embryogenesis, with higher levels accumulating in the brain, midgut primordia, and VNC. A maternally inherited role for *InR* is reflected by abundant *InR* mRNA in nurse cells and mature oocytes (Petruzzelli et al. 1986; Garofalo and Rosen 1988). Accordingly, embryonic lethality is associated with *InR* complete loss-of-function mutations whereas some heteroallelic combinations yield animals that are viable but sterile (Fernandez et al. 1995; Chen et al. 1996; Tatar et al. 2001). Viable embryos lack neuroblasts and are unable to complete germband retraction and dorsal closure. They display abnormal head structures and cuticle. Moreover, mutant embryos display defects in VNC condensation and commissure formation. *InR* expression persists in the nervous system during larval stages, and is detected in all imaginal discs and postsynaptically at neuromuscular junctions (NMJs) (Garofalo and Rosen 1988; Gorczyca et al. 1993; Fernandez et al. 1995). InR is enriched in photoreceptor axons of late larvae (Song et al. 2003). In adults, *InR* mRNA is predominantly localized to the brain cortex, cells of the thoracic and abdominal ganglia, and the gut (Veenstra et al. 2008).

Small animals result from reduced InR activity (Fernandez et al. 1995; Chen et al. 1996; Brogiolo et al. 2001; Tatar et al. 2001). Organismal size is additionally affected by alteration of conserved InR signaling pathway components. Positive regulators downstream from InR include: the insulin receptor substrate (IRS) ortholog Chico (Böhni et al. 1999), the PI3K sub-

units PI3K92E and PI3K21B (Weinkove et al. 1999), the PI-dependent protein kinase Pdk1 (Rintelen et al. 2001), and the kinases Tor (Oldham et al. 2000), Akt1 (Verdu et al. 1999), and S6K (Montagne et al. 1999) (Fig. 4). Negative regulators downstream from InR include: the phosphatase Pten (Gao et al. 2000; Oldham et al. 2002), the tuberous sclerosis genes *Tsc1* and *Gigas*/*Tsc2* (Gao and Pan 2001; Potter et al. 2001), and the transcription factor Foxo (Jünger et al. 2003). Cell-autonomous effects of InR on cell size and number rely on kinase activity (Brogiolo et al. 2001) and are antagonized by *Pten* overexpression (Huang et al. 1999), coexpression of *Tsc1* and *gigas* (Potter et al. 2001), or reduced Pdk1 activity (Rintelen et al. 2001). Although *PI3K92E* or *Akt1* overexpression increases cell size it fails to influence cell number or division (Verdu et al. 1999; Weinkove et al. 1999), substantiating the supposition that InR serves two independent functions: to promote proliferation via Ras/ERK and to promote protein synthesis through PI3K (Oldham et al. 2002). The list of genes contributing to body size determination and functioning downstream from InR continues to grow and to date includes numerous conserved and *Drosophila*-specific factors.

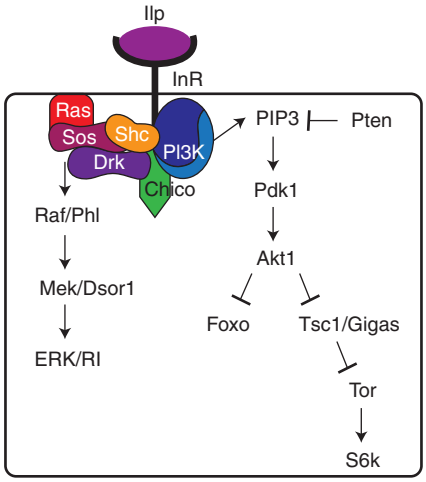

Figure 4. Ubiquitous InR signaling. Interaction of InR with its Ilp ligand induces InR autophosphorylation. Chico interacts directly with the phosphorylated receptor, recruiting PI3K along with a multitude of other factors including adaptor proteins and downstream effectors. InR promotes proliferation via canonical Ras/Raf/Mek/ERK signaling and growth via the activation of Akt1. Akt1 stimulates protein synthesis by activating downstream kinases Tor and S6K, and by inhibiting Foxo nuclear accumulation and transcriptional activity.

Seven insulin-like peptides (Ilp1-7), InR ligands, are differentially expressed among *Drosophila* developmental stages and tissues: *Ilp2*, *Ilp4*, and *Ilp7* are expressed in the mesoderm and midgut; *Ilp1*, *Ilp2*, *Ilp3*, and *Ilp5* are expressed in neurosecretory cells of the brain that project to the ring gland, heart and brain lobes, and foregut; *Ilp2* is expressed in imaginal discs and salivary glands; *Ilp7* is expressed in neurons of the ventral ganglion, a subset of which innervates the adult hindgut and another that makes synaptic contact with *Ilp1*,*2*,*3*,*5*-expressing neurosecretory cells; *Ilp5* is expressed in ovarian follicle cells; *Ilp3* is expressed in adult midgut muscle; and *Ilp6* is expressed in the FB, gut, and in CNS surface glia (Gorczyca et al. 1993; Brogiolo et al. 2001; Ikeya et al. 2002; Rulifson et al. 2002; Broughton et al. 2005; Miguel-Aliaga et al. 2008; Veenstra et al. 2008; Okamoto et al. 2009; Slaidina et al. 2009; Chell and Brand 2010; Cognigni et al. 2011). *Ilp* overexpression increases organismal size by stimulating cell growth and division (Brogiolo et al. 2001; Ikeya et al. 2002; Slaidina et al. 2009). FB-specific activation of InR promotes triglyceride storage, by increasing fat cell number and lipid content (DiAngelo and Birnbaum 2009). Reciprocally, ablation of *Drosophila Ilp*-expressing neurons causes developmental delays, a reduction in egg production rates, and a reduction in organismal size owing to decreased cell number and size (Ikeya et al. 2002; Rulifson et al. 2002; Broughton et al. 2005). In addition to developmental disparities, flies devoid of Ilp-producing neurons have elevated levels of glucose and trehalose, like *InR* and *chico* mutants.

Although the InR-signaling pathway autonomously influences growth and proliferation, it nonautonomously influences aging. Long-lived animals result from reduced activity of InR, Chico, Tor, and S6K (Clancy et al. 2001; Tatar et al. 2001; Kapahi et al. 2004). Although nutritional starvation during larval stages influences

organismal size and fecundity, it is insufficient to influence aging (Tu and Tatar 2003). Dietary restriction in adults, however, promotes longevity and correlates with reduced *Ilp5* mRNA levels (Min et al. 2008). Ablation of Ilp-producing neurosecretory cells can also extend lifespan (Broughton et al. 2005).

Recently, both the reactivation of proliferation in quiescent embryonic neuroblasts and the elimination of larval neuroblasts postpupariation were shown to correlate with InR signaling. The reception by quiescent embryonic neuroblasts of "nutritional adequacy" signals from the FB elicits *Ilp* expression in glial cells, activating InR and proliferation in quiescent neuroblasts in a paracrine manner (Britton and Edgar 1998). This reactivation of InR relies on Tor and the amino acid transporter Slimfast (Slif) in the FB, and functional InR/PI3K/Akt/Tor in neuroblasts. Consistent with InR promoting proliferation and survival, InR activation in combination with proapoptotic gene ablation delays larval neuroblast elimination. Reduced InR signaling, on the other hand, promotes larval neuroblast elimination postpupariation. In light of observations wherein impaired autophagy enhances caspase-dependent neuroblast survival, Foxo is proposed to activate autophagy in aging neuroblasts (Chell and Brand 2010; Siegrist et al. 2010; Sousa-Nunes et al. 2011). This is consistent with the acknowledged antagonism between autophagy and insulin signaling pathways (Chang et al. 2009) and the proposed mechanism of lifespan extension by Foxo in muscle (Demontis and Perrimon 2010). It is plausible that two other genes in the *Drosophila* genome, *CG3837* and *CG10702*, predicted to encode for insulin-like receptors (Table 1), play a role in this context given that elevated levels of the corresponding proteins have been detected in salivary glands undergoing autophagic programmed cell death (Martin et al. 2007).

In addition to growth and longevity, InR also impinges on reproduction. *InR* mutant eggs chambers, unable to interpret both follicular cell-derived and systemic insulin signals, are developmentally delayed owing to impaired vitellogenesis and cyst growth. InR, deficient germline stem cells (GSCs) show reduced division rates owing to compromised G_2 phase of the GSC division cycle, whereas hindered GSC division in *InR* mutant females reflects additional effects on Notch activity and E-cadherin-mediated adhesion within the niche (Drummond-Barbosa and Spradling 2001; LaFever and Drummond-Barbosa 2005; Hsu et al. 2008; Yu et al. 2009; Hsu and Drummond-Barbosa 2011). An analogous scenario exists in the male germline: insulin signaling in germ and support cells promotes spermatocyte growth and maintains cyst numbers by promoting G_2/M phase progression of GSCs (Ueishi et al. 2009; McLeod et al. 2010).

Ilps are expressed in synaptic boutons at the presynaptic terminals of larval body wall muscles (Gorczyca et al. 1993). Overexpression of *PI3K92E*, *Akt* or *InR*, specifically in larval motor neurons, induces supernumerary synapses projecting to each body wall muscle whereas reduced PI3K or Akt activity reduces synapse number. Similar effects are seen in projection neurons of the brain. Alterations of PI3K activity in motor and projection neurons elicits modified locomotive behaviors (Martin-Pena et al. 2006).

InR mutants display defects in photoreceptor axon path finding reminiscent of animals deficient for *Dystroglycan* and *Dystrophin*—two genes linked to muscular dystrophies. *InR* interacts genetically with *Dystroglycan* and is speculated to function independently of Chico and the PI3K/Akt pathway in this context, and instead associates with the Dg-Dock-Pak pathway to guide neuronal migration (Song et al. 2003; Shcherbata et al. 2007).

Alk: An RTK Involved in the Development of the Visceral Mesoderm, as Well as Motor and Visual Circuitry

Alk is required for the generation of visceral mesoderm—cells that will comprise the inner circular muscles and outer longitudinal muscles that ensheath the intestinal tract. *Alk* deficient embryos are unable to specify visceral mesoderm founder cells and completely lack visceral musculature. *Alk* mutants lack intestinal structures, do not eat and die at the first instar larval

stage (Englund et al. 2003; Lee et al. 2003; Lorén et al. 2003).

The derivation of mesoderm in *Drosophila* relies on the coordinated activity of Dpp, Hedgehog (Hh) and Wg. Signaling in these pathways is mediated by Tinman, a conserved homeodomain transcription factor required for somatic, cardiac and visceral mesoderm development (Azpiazu and Frasch 1993; Bodmer 1993; Furlong 2004). A screen for Tinman targets identified *jelly belly (jeb)*. *jeb* is expressed in early ventral and medial somatic mesoderm cells, adjacent to *Alk*-expressing visceral mesoderm cells. Only visceral mesoderm is affected in *jeb* mutants; ergo, the logical gene name—*jelly belly*—referring to a jiggly expansive abdomen and lack of midgut muscles (J Weiss, pers. comm.). The *jeb* mutant phenotype is akin to that of *Alk* and is reflective of a failure of visceral mesodermal cells to differentiate and migrate, because of a lack of either Jeb secretion by ventral somatic mesoderm precursor cells or Jeb engagement by Alk at visceral muscle precursors (Weiss et al. 2001; Stute et al. 2004). Engagement of Alk by Jeb activates ERK in visceral muscle progenitors to establish two separate pools of cells: founder myoblasts and fusion-competent myoblasts. In the absence of *jeb* or *Alk*, all visceral mesoderm progenitors become fusion-competent myoblasts and these cells fuse with the somatic muscle founders because founder myoblasts are nonexistent, resulting in a complete lack of visceral musculature (Stute et al. 2004). Ectopic expression of activated Alk in the visceral mesoderm restores gut morphogenesis to *jeb* mutants by reinstating expression of genes downstream from ERK: *dumbfounded*, *org-1*, *sticks and stones*, *Hand*, and *Dpp* (Englund et al. 2003; Lee et al. 2003; Stute et al. 2004; Varshney and Palmer 2006; Shirinian et al. 2007).

A proposed function for Alk in neuronal development is based on conserved nervous system expression in *C. elegans*, mouse, and chick (Iwahara et al. 1997; Liao et al. 2004; Hurley et al. 2006; Vernersson et al. 2006; Reiner et al. 2008). Like *Alk*, *jeb* is expressed in a subset of neurons distributed throughout the VNC in late *Drosophila* embryogenesis. The accumulation of Jeb in CNS axons is dependent on Alk (Englund et al. 2003; Lee et al. 2003; Stute et al. 2004; Rohrbough and Broadie 2010). Further, postsynaptic Jeb internalization and Alk accumulation at developing NMJs during embryonic and larval stages is regulated by Mind the gap (Mtg), a neuronally secreted glycoprotein required for synaptic cleft extracellular matrix assembly. Rescue of defective *jeb* mutant larvae locomotion by neuronal-specific *jeb* expression unveiled a neuronal requirement for Jeb (Rohrbough and Broadie 2010).

During pupal stages, Alk functions in the visual system in photoreceptor axon target selection. *jeb* is expressed in photoreceptor axons, whereas *Alk* is expressed in processes of target neurons innervating the optic lobe. Photoreceptor axons secrete Jeb to activate Alk in target neurons within the lamina and medulla. R7 and R8 photoreceptor axons are significantly altered when Alk is removed from target neurons (Bazigou et al. 2007). *jeb* mosaic animals also show photoreceptor projection targeting defects. These photoreceptor navigation errors are reflective of a lack of regular lamina cartridge patterning and defective *duf* expression (Englund et al. 2003; Lee et al. 2003; Stute et al. 2004).

Olfactory learning deficits are associated with Alk activation and surprisingly elevated performance correlates with Alk inactivation. In addition to impaired learning, animals bearing constitutive Alk activation are small and conversely animals deficient for Alk activity are large. These nonautonomous effects on organismal size rely on the activation of Alk in peptidergic and cholinergic neurons and are insulin independent. *Alk* displays genetic interactions with the Ras GTPase activating protein *Nf1*. Consistent with the genetics, Alk activates ERK whereas Nf1 functions as a negative regulator of ERK (Walker et al. 2006). These antagonistic roles for Alk and Nf1 are proposed to regulate the release of GABA neurotransmitter and account for learning and long-term potentiation phenotypes (Ho et al. 2007; Liu et al. 2007).

Alk plays a vital role in protecting the developing CNS from nutrient deprivation. Under these conditions, flies eclose with relatively small bodies. Their heads, however, are of normal size. This is because nutrient deprivation

triggers Jeb secretion from glia, activating Alk in the neural progenitors of the brain. Alk stimulates the activation of the InR effectors S6K, Thor, and PI3K, specifically in the brain, salvaging it from nutrient restriction (Cheng et al. 2011). This mechanism is Ras independent and therefore distinct from that described for Alk elsewhere. Of all *Drosophila* RTKs, Alk shares the most sequence similarity with InR. Mammalian ALK binds IRS-1 and SHC via its NPXpY motif. This motif exists in *Drosophila* Alk and offers a mechanism by which Alk activates PI3K when nutrients are limiting (Fujimoto et al. 1996).

THE TRK SUPERFAMILY OF RTKs: Ror, Nrk, AND DDR

Ror: A *Drosophila* Orphan RTK with Roles Exclusively in the Nervous System

Although *Drosophila* Ror is most similar to human Ror1 and Ror2 (~35% identity), it lacks many of the domains found in the human Ror RTKs. *Ror* expression begins ~6.5 hr after fertilization and peaks between 8–12 hr. *Ror* is expressed exclusively in neurons of the CNS and PNS (Wilson et al. 1993). This time in *Drosophila* development coincides with neural differentiation and axonogenesis and as such Ror is suggested to be involved in these processes. Consistent with this, the *C. elegans* Ror ortholog CAM-1 regulates neuronal polarity and the asymmetric division of neurons (Forrester et al. 1999) and vertebrate Rors play roles in neurite outgrowth and synapse formation (Paganoni and Ferreira 2005; Paganoni et al. 2010). A mutant phenotype for *Ror* in *Drosophila*, however, has not been described.

Ror shows a pattern of cysteine residue spacing suggestive of ligand binding like that for other transmembrane receptors such as Frizzled (Fz) (Saldanha et al. 1998). Like Fz, this region binds Wnt ligands in *C. elegans*, *Xenopus*, and mammalian cell lines (Hikasa et al. 2002; Oishi et al. 2003; Mikels and Nusse 2006; Green et al. 2007). The interaction of Ror proteins with various Wnts has been implicated in diverse contexts including: the migration and asymmetric division of neurons and vulval precursor cells in *C. elegans*, convergent extension in *Xenopus*, mouse embryonic fibroblast migration, and synapse formation in the mouse brain (Green et al. 2008; Grumolato et al. 2010; Paganoni et al. 2010). To date, Ror binding to Wnt has not been reported in *Drosophila*.

Neurotropic Receptor Kinase: Another *Drosophila* Orphan RTK in the Nervous System

Neurotropic receptor kinase (Nrk) is considered a MuSK ortholog, based on extensive homology in its kinase domain (Sossin 2006). Like Ror RTKs, MuSK binds Wnt ligands via the Fz domain (Jing et al. 2009). Although differences exist between Nrk and MuSK extracellular domains, Nrk has an Fz domain and is predicted to bind Wnts. In vertebrates, MuSK induces acetylcholine receptor clustering at NMJs and the stability of clusters relies on the heparan–sulphate proteoglycan Agrin and LRP coreceptor (DeChiara et al. 1996; Bezakova et al. 2001; Kim et al. 2008; Zhang et al. 2008). Nrk, however, lacks the extracellular domains responsible for Agrin binding as well as the intracellular NPXpY motif in MuSK essential for NMJ formation (Herbst and Burden 2000). MuSK has an Agrin-independent role in axon guidance in zebrafish (Zhang et al. 2004) and a noncanonical Wnt-mediated function in neural crest cell migration in mouse (Banerjee et al. 2011). These studies hint at similar roles for Nrk.

Nrk expression begins ~9.5 hr after fertilization, shortly after the determination of neural precursor cells. Expression of *Nrk* is initially detected in the neuroectoderm and becomes restricted to neural progenitor cells situated between epidermal and mesodermal cell layers. Expression persists in the neural cell lineage throughout embryogenesis and peaks again at the pupal stage during restructuring of the nervous system (Oishi et al. 1997). In support of a role for Nrk in the nervous systems, *Nrk* expression was down-regulated in embryos for which neuroectoderm was derived primarily from glial cells, rather than both neurons and glia (Egger et al. 2002).

Discoidin Domain Receptor: A Poorly Characterized RTK in *Drosophila*

Discoidin domain receptors (DDR) are atypical RTKs in that they are activated by collagen rather than secreted factors. Moreover, maximal activation of DDRs occurs several hours after collagen binding, unlike other RTKs that are activated within minutes of receptor engagement (Shrivastava et al. 1997; Vogel et al. 1997). Although *Drosophila* Ddr has not yet been shown to bind collagen, conservation of the discoidin domain suggests that it should possess this ability (Sossin 2006). DDRs have been implicated in cell migration, extracellular matrix remodeling, proliferation and differentiation in a number of tissues including vertebrate lung, skin, GI tract, kidney, heart, liver, mammary gland, endometrium, and brain (Vogel et al. 2006). Like its mammalian counterparts, the sole *Drosophila* Ddr bears an extensive number of tyrosine residues in its cytoplasmic region. In mammals, these residues recruit a number of downstream factors following phosphorylation including Shc, Nck2, Shp-2, PI3K, RasGAP, and Stats (Lemeer et al. 2011). Wnt5a was shown to be required for collagen-induced activation of DDR in a breast cancer cell line (Jonsson and Andersson 2001). It is tempting to speculate that Wnt5A might function as a ligand for DDR, in a manner analogous to that of Ror and Ryk RTKs.

OFFTRACK: A "DEAD" RTK WITH ROLES IN MOTOR AND CNS AXON TARGETING AND EMBRYONIC PATTERNING

Drosophila off-track (also known as *Dtrk*) shares 65% similarity with human Trk. *off-track* (*otk*) is expressed 3–4 hr postfertilization in the anterior midgut primordia, the cephalic furrow, and along the germ band. Expression peaks mid-embryogenesis in neuroectodermal cells and internalized CNS neuroblasts. Otk expression persists in prospective gut and head regions, and eventually accumulates throughout the CNS in segmentally repeated commissures, in axon bundles exiting the CNS, in motor neuron projections innervating muscle fibers, and in neurons of a subset of sensory organs. Notably, *otk* null animals are embryonic lethal (Pulido et al. 1992; Winberg et al. 2001).

Otk bears structural similarity with cell adhesion molecules of the immunoglobulin (Ig) superfamily expressed in the *Drosophila* nervous system. Like other Ig superfamily members, Otk is glycosylated and permits cell aggregation in vitro (Pulido et al. 1992). This property likely influences neuroblast migration and axon targeting. Accordingly, Otk is implicated in Sema-1a-mediated embryonic motor and CNS axon guidance based on: (1) its physical association with the repulsive axon guidance receptor Plexin A; (2) impaired defasciculation and disrupted axon morphology and targeting in *otk* mutant embryos, similar to that resulting from Sema-1a or PlexA inactivation; and (3) genetic interactions between *otk* and *PlexA* or *Sema-1a* (Pulido et al. 1992; Winberg et al. 2001). Conserved catalytic residues in the kinase domain are altered in Otk and as such Otk belongs to the CCK-4 subfamily of "dead" RTKs (Kroiher et al. 2001). Otk itself is tyrosine phosphorylated, which may serve to recruit signaling molecules to a Sema-1a-PlexA-Otk complex (Pulido et al. 1992; Winberg et al. 2001).

A screen for R1–R6 photoreceptor growth cone targeting identified *otk*; an increased number of R1–R6 photoreceptor axons project through the lamina and inappropriately into the medulla of the developing larval optic lobe in *otk* mosaic heads. The role of Otk in guiding R1–R6 axons appears to be unrelated to that of Otk in Sema-1a signaling (Cafferty et al. 2004). The Otk ligand responsible for R1–R6 targeting is unknown.

Recently, Otk binding to Wnt4 was shown to inhibit canonical β-catenin/TCF signaling in an Fz-dependent but LRP-independent manner. Both *otk* and *Wnt4* mutants show embryonic patterning defects indicative of excessive canonical β-catenin/TCF signaling. In the ventral embryonic epidermis and the adult wing, *otk* and *Wnt4* overexpression reduce canonical β-catenin/TCF signaling. Ectopic *Wnt4* expression phenotypes rely on functional Otk and synergizes with *otk* overexpression. Otk is postulated to direct noncanonical Wnt signaling

through interaction with Disheveled, and inhibit canonical Wnt signaling by either occluding LRP or by sequestering canonical Wnts (Peradziryi et al. 2011).

THE RYK SUPERFAMILY OF RTKs: DERAILED AND DOUGHNUT

Derailed: Another "Dead" RTK with Roles in Neuronal Pathway Selection and Muscle Attachment

derailed (drl) expression begins ~6 hr postfertilization, in the embryonic epidermis and in salivary placodes. By 10 hr, Drl is detected in somatic muscle 21–23 precursors and their associated epidermal cells. By 12 hr, *drl* expression is detected in a subset of heterogeneous neurons that project in the anterior commissure (AC) of the VNC (Callahan et al. 1995, 1996; Bonkowsky and Thomas 1999; Harris and Beckendorf 2007). *drl* is expressed later in the larval CNS, as well as the adult brain. Homozygous *drl* mutant animals are viable but uncoordinated because of *drl* axon mistargeting and defasciculation, and the inability of muscles 21–23 to establish functional attachments with the epidermis. *drl* mutant animals show additional learning and memory defects as a consequence of structural defects of the adult brain (Bolwig et al. 1995; Dura et al. 1995; Moreau-Fauvarque et al. 1998; Simon et al. 1998; Grillenzoni et al. 2007; Sakurai et al. 2009).

RYK proteins interact with Wnt5, the cognate ligand for the transmembrane protein Fz. Wnt5 functions as a repulsive signal for Drl during embryogenesis, directing Drl-expressing axons away from the posterior commissure (PC) and toward the AC of each VNC hemisegment (Fradkin et al. 2004). Uncoordinated *wnt5* mutants display axon navigation and axon fasciculation defects similar to *drl* mutant animals. Further, AC loss following *wnt5* overexpression in the midline is dependent on functional Drl. Moreover, both *drl* and *wnt5* mutants show alterations in dendritic branching of CNS serotonergic neurons (Singh et al. 2010). Like Drl, mammalian Wnt5a routes RYK expressing axons through the corpus callosum (Keeble et al. 2006) and corticospinal tract (Liu et al. 2005). Unlike mammal RYK (Lu et al. 2004), however, Drl does not impact on canonical Wnt/β-catenin signaling (Wouda et al. 2008) and the activity of *Drosophila* Wnt5 in PC repulsion appears independent of Fz (Yoshikawa et al. 2003). Interestingly, *wnt5* itself appears to be a target of Drl-activated neurons (Fradkin et al. 2004; Yao et al. 2007).

Drl and Wnt5 positively regulate glutamatergic NMJ development and synaptic transmission. Both *drl* and *wnt5* mutants have reduced numbers of synaptic boutons and reduced NMJ size (Liebl et al. 2008). Growth of the NMJ during larval stages requires coordination between the presynaptic motor neuron and postsynaptic muscle (Zito et al. 1999). *drl* mutant phenotypes at NMJs are rescued by muscle-specific expression of *drl*, whereas Wnt5 functions exclusively in presynaptic motor neurons. Reducing *drl* dosage suppresses NMJ overgrowth resulting from *wnt5* neuronal overexpression, implicating Drl downstream from Wnt5. Further, rescue of *drl* phenotypes with exogenous Drl requires the WIF (Wnt-inhibitory-factor) domain. This evidence suggests that Wnt5 released from the presynaptic boutons binds Drl on postsynaptic muscle to regulate bouton growth and postsynaptic differentiation (Liebl et al. 2008).

Src64B and *Src42A* mutants show defects in mushroom body (MB) anatomy, salivary gland development, and AC formation similar to *Wnt5* and *drl* mutants. *Src64B* interacts genetically with *drl*, as well as *Wnt5*, in MB development, salivary gland migration, and VNC neuron commissure formation (Nicola et al. 2003; Harris and Beckendorf 2007; Wouda et al. 2008). RYK proteins bear alterations in conserved catalytic residues required for phosphotransfer and are therefore inactive (Katso et al. 1999; Yoshikawa et al. 2001). Rather, Src64B functions as the TK responsible for Drl phosphorylation and interaction with Drl stimulates Src64B activity. Src64B is likely responsible for Wnt5/Drl-mediated axon repulsion, given that Drl-dependent axon pathfinding relies on Src64B kinase activity. Drl is proposed to provide substrate specificity for Src proteins (Wouda et al. 2008).

The learning and memory defects of *drl* mutant animals are likely a consequence of Wnt5 regulating olfactory circuitry. A subset of *drl*-expressing cells normally antagonizes Wnt5 produced by olfactory receptor neurons (ORNs) to appropriately pattern and orient glomeruli during antennal lobe development. This function of Drl relies on the WIF domain (Fradkin et al. 2004; Yao et al. 2007). Delineation of the functional requirement of *drl* in the antennal lobe refined cell-type identities to lateral neuroblast and ventral neuroblast-derived neurons (Bolwig et al. 1995; Dura et al. 1995; Moreau-Fauvarque et al. 1998; Simon et al. 1998; Grillenzoni et al. 2007; Sakurai et al. 2009). *drl* mutant phenotypes of the olfactory system resemble those resulting from *wnt5* overexpression in ORNs: aberrant positioning of glomeruli and ectopic targeting of ORN axons to extraneous glomeruli structures. Moreover, enhancement or attenuation of Wnt5 function can either exacerbate or suppress *drl* phenotypes respectively (Fradkin et al. 2004; Yao et al. 2007).

A similar antagonistic relationship between *drl* and *wnt5* exists in MBs. Pan-neuronal *drl* overexpression phenocopies *wnt5* loss-of-function and attenuation of Drl activity can suppress *wnt5* overexpression phenotypes. Neuronal *drl* expression is sufficient to nonautonomously rescue MB defects in *drl* mutants whereas *wnt5* expression in MBs restores MB morphology to *wnt5* mutants. These data suggest that Drl-dependent sequestration of Wnt5 is required to limit MB axonal growth (Bolwig et al. 1995; Dura et al. 1995; Moreau-Fauvarque et al. 1998; Simon et al. 1998; Grillenzoni et al. 2007; Sakurai et al. 2009).

Doughnut on 2: An RTK Involved in Migration

drl and *doughnut on 2* (*dnt*) likely arose by gene duplication because the two genes display more similarity to each other than mammalian RYKs. Although Drl and Dnt share 60% identity, *dnt* cannot completely rescue *drl* mutant phenotypes (Oates et al. 1998). Maximal expression of *dnt* occurs 4–6 hr postfertilization, 2 hr before maximal *drl* expression; however, expression of both persists throughout the *Drosophila* life cycle (Roy et al. 2010). Like Drl, Dnt is considered catalytically inactive, based on substitutions of critical catalytic amino acids in the TK domain.

dnt is expressed initially in the central region and anterior domain of the embryo. Later expression occurs primarily in invaginating cells of the ventral furrow, gut, cephalic, and transverse furrow, and tracheal pits. The name *doughnut* comes from the rings of expression surrounding tracheal primordia (Oates et al. 1998; Savant-Bhonsale et al. 1999). *dnt* plays a minor role, with *drl* and *Drl-2*, in salivary gland cell migration during late embryogenesis (Harris and Beckendorf 2007). Disruption of the *dnt* locus influences multiple body size-related traits including face and head width, thorax length and wing size (Carreira et al. 2008). Although the disparate expression patterns of *dnt* and *drl* are indicative of paralogous function, to date relatively little characterization of *dnt* has substantiated this conjecture.

Derailed 2: An RTK Sharing Overlapping Roles with DRL in Olfactory Circuitry and Salivary Gland Migration

Derailed 2 (Drl-2) shares 35% identity with Drl, yet the two share distinct expression patterns and *drl-2* mutants display relatively mild defects in antennal lobe development compared with *drl*: one of two displaced glomeruli displayed defects similar to *wnt5* and *drl* mutants whereas the other was similar only to that of *wnt5* and opposite to that of *drl* mutants. *drl* and *drl-2* mutant alleles synergize in this context; a *drl drl-2* double mutant displays additional defects resembling *wnt5* mutants, implicating Drl-2 in Wnt5 signaling. Further, ORN-specific overexpression of *wnt5* bears little effect in a *drl-2* mutant or *drl drl-2* double mutant background. Glial-specific expression of *Drl-2* can compensate for loss of *drl* suggesting that these receptors have paralogous functions in Wnt5 signaling dependent on cell context (Bolwig et al. 1995; Dura et al. 1995; Moreau-Fauvarque et al. 1998; Simon et al. 1998; Grillenzoni et al. 2007; Sakurai et al. 2009).

Wnt5 in the CNS repels *drl*-expressing salivary gland tip cells, thereby dictating salivary gland migration. In this context, *drl-2* mutants show similar defects to *drl* mutants: ventromedial curving of tip cells and a failure of visceral mesoderm attachment. *drl drl-2* double mutant embryos phenocopy *drl* mutants, indicating that Drl-2 plays a minor role in salivary gland morphogenesis (Harris and Beckendorf 2007). Drl-2 has a similar role to Drl in the development of the larval and embryonic musculature; however, in this case *drl-2* expression in specific motor neurons functions in preventing synapse formation with inappropriate ventral muscles (Inaki et al. 2007).

RET: THE HOMOLOG OF THE MAMMALIAN RTK PROTO-ONCOGENE RET

Ret expression begins ~3.5 hr postfertilization in scattered regions throughout the yolk sac and is not detected again until 5–7 hr, in a subset of neuroblasts. At ~10 hr, *Ret* is expressed in midline glia of the VNC, in the somatogastric nervous system anlage, in midgut precursor cells, and transiently in the malpighian tubule anlage. Late expression is observed in the developing PNS and CNS (Sugaya et al. 1994; Hahn and Bishop 2001; Fung et al. 2007). During larval stages, *Ret* is expressed in neuroendocrine cells of the brain and ventral ganglion, as well as in leg, wing, antennal, and eye imaginal discs (Hahn and Bishop 2001; Read et al. 2005). This expression pattern is similar to that of human RET, the closest vertebrate homolog of *Drosophila* Ret (52% identity in the TK domain).

The ligand for vertebrate RET, glial cell line-derived neurotrophic factor (GDNF), does not bind RET, but rather the GPI-linked coreceptor GFR-α. Although *Drosophila* Ret shares homology and structural organization in its extracellular domain with that of vertebrate RET, a homologous GDNF ligand or GPI-linked receptor does not exist in the *Drosophila* genome (Anders et al. 2001). Furthermore, *Drosophila* Ret does not bind GDNF. Rather, four extracellular cadherin-like domains suggest an ancient role for Ret in adhesion, although *Drosophila* Ret is incapable of self-association in vitro (Abrescia et al. 2005).

A Ret transgene with equivalent mutations to that observed in multiple endocrine neoplasia (MEN) expressed in the *Drosophila* eye caused phenotypes analogous to that in vertebrates: excessive proliferation and aberrant neuronal specification. In accordance with a proposed role for Ret in cell adhesion, deficiencies in the adhesion regulators *Moe*, *Pax*, and *Cad-N2*-enhanced Ret^{MEN}-dependent phenotypes (Hahn and Bishop 2001; Read et al. 2005). These phenotypes were further modulated by mutation of Ras, Src, and JNK, consistent with characterized roles for human RET (Arighi et al. 2005). Defective eye development induced by Ret^{MEN} expression was altered by DJ-1α/β—proteins linked to Parkinson's disease—likely by modulating Ras/ERK signaling (Aron et al. 2010).

Cad96Ca: A CADHERIN DOMAIN-CONTAINING RTK INVOLVED IN WOUND REPAIR

Like Ret, Cad96Ca (also known as Stitcher) has both cadherin and TK domains (Tepass et al. 2000). *Cad96Ca* is expressed in all ectodermal epithelia during mid- and late embryonic stages but later becomes restricted to the epithelial optic lobe anlagen (Fung et al. 2007). Homozygous *cad96C* null animals die at late pupal stages. Cad96Ca displays TK activity in vitro, and a functional TK domain is required for rescue of *Cad96Ca* mutant animals (Wang et al. 2009).

Cad96Ca is predicted to play a role in nervous system development given that *Cad96Ca* expression was found down-regulated in late-stage embryos for which neuroectoderm was derived from glial cells (Egger et al. 2002). Consistent with this, many classical cadherins are expressed in the developing nervous system and have roles in neurite outgrowth, and axonal patterning and fasciculation (Tepass et al. 2000).

Cad96Ca is expressed in primordia of the spiracle—the external opening of the larval respiratory system—where it reinforces DE-Cad activity in posterior spiracle morphogenesis.

Expression of *Cad96Ca* in this context depends of EGFR and Hh signaling, as well as the transcription factor Cut (Lovegrove et al. 2006; Maurel-Zaffran et al. 2010).

Cad96Ca facilitates embryonic re-epithelialization following wound healing by stimulating actin cable formation and the transcription of cuticle repair genes by the transcription factor Grh (Wang et al. 2009). Moreover, Cad96Ca can induce ERK phosphorylation, which is required for Grh activation (Mace et al. 2005).

Eph: AN RTK INVOLVED IN AXON PATHFINDING

Drosophila Eph displays similarity to both classes of vertebrate Eph receptors (~35% in the extracellular region and 71% in the TK domain), whereas the best characterized ligand for Eph in *Drosophila*, Ephrin, shares ~40% identity in the extracellular ephrin domain with both classes of human ephrin ligands (Bossing and Brand 2002).

Eph is expressed exclusively in the nervous system, initially in the neuroectoderm ~5 hr postfertilization and then after ~10 hr in a subset of neurons of the brain and VNC. Expression persists in the larval CNS and MBs, photoreceptor axonal projections and developing optic ganglia. Eph protein localizes to axons of elongating neurons, with highest concentrations in the growth cones of the earliest differentiating cortical and MB neurons and photoreceptors, and on longitudinal and commissural axons of the VNC (Scully et al. 1999; Dearborn et al. 2002; Boyle et al. 2006). This localization is proximal to that of Ephrin, which is concentrated in neuronal cell bodies along the outer edge of connectives and between commissures (Bossing and Brand 2002).

Disruption of *Eph* function by RNAi results in defective projection of photoreceptor axons as well as the aberrant targeting and loss of medulla and lobular cortical axons. *Eph* function is required specifically at the visual system midline to direct axon targeting in the developing eye and optic ganglia. Eph is predicted to fulfill a comparable role in the VNC; RNAi-mediated disruption of *Eph*, as for *Ephrin*, results in commissure fusion and loss, in addition to connective fragmentation as a consequence of interneuronal axon departure from the CNS longitudinal connectives. *Ephrin* expression at the midline, on the other hand, repels contralateral axon midline crossing and halts axonal growth along connectives, in an Eph-dependent manner. *Eph* null animals are viable and display abnormalities specifically in projection neuron targeting during MB development (Scully et al. 1999; Dearborn et al. 2002; Boyle et al. 2006). Additional phenotypes uncovered for *Eph* in other studies may reflect unintentional RNAi-mediated targeting of homologous targets.

Drosophila Vap33 is a proposed alternative ligand for Eph. Like Ephrin, Vap33 is membrane anchored and *vap33* null mutants display MB defects in late pupae and adult brains identical to those of *Eph*. Moreover, inactivation of *Eph* can suppress muscular defects resulting from neuronal Vap33 expression. Vap33 can bind to the extracellular domain of *C. elegans* VAB-1 Eph receptor. This binding appears conserved among VAP proteins and is proposed to antagonize Ephrin binding (Tsuda et al. 2008).

Finally, *Drosophila* Ephexin (Exn) like its vertebrate Rho-type guanine nucleotide exchange factor counterpart binds Eph, at NMJs. Exn binds the Eph TK domain via its SH3 and Rho-GEF domains. Exn is required at the presynaptic nerve terminal of the NMJ to modulate synaptic vesicle release; disruption of either *Exn* or *Eph* interferes with homeostatic compensatory neurotransmitter release at NMJs. Eph is hypothesized to serve as a presynaptic receptor for a muscle-derived retrograde signal, speculated to be either Ephrin or Vap33 (Frank et al. 2009).

PDGF- AND VEGF-RECEPTOR RELATED: AN RTK WITH ROLES IN TISSUE SCULPTING, CELL MIGRATION, AND SURVIVAL

PDGF- and VEGF-receptor related (Pvr) is expressed ~4 hr postfertilization in the procephalic mesoderm. Expression is later restricted to populations of scattered hemocytes, the hematopoietic cells in *Drosophila*. Three Pvr ligands, Pvf1-3, are expressed along stereotypical

routes taken by migrating hemocytes. Although nonessential for differentiation, Pvr is required cell-autonomously for maintaining migrating populations of mature hemocytes. Pvr/Pvf induces ERK activation and hemocyte migration and is dependent on Ras1 (Heino et al. 2001; Cho et al. 2002; Brückner et al. 2004).

Plasmatocytes represent the majority class of hemocytes. They are phagocytic, clearing apoptotic debris generated during the programmed cell death that is necessary for tissue sculpting and metamorphosis (Tepass et al. 1994). *Pvr* mutant embryos show CNS axon scaffolding and glial cell positioning defects, as a consequence of reduced hemocyte numbers and therefore compromised neuron and glial cell elimination (Sears et al. 2003). They also show defective VNC condensation resulting from reduced hemocyte-derived extracellular matrix (Olofsson and Page 2005). Pvr is present in midline glia (MG) and all Pvf ligands localize to midline neurons of the CNS. Pvr/Pvf maintain and direct MG during embryogenesis; expression of activated Pvr at the midline induces enlargement of MG clusters and misallocated supernumerary MG, whereas ectopic *Pvf* expression at the midline or specifically in neurons reroutes MG migration. In the absence of functional Pvr, MG are disorganized or lost because of excessive apoptosis (Learte et al. 2008).

Embryonic plasmatocytes found larval hemocyte populations and self-renewal requires an intact PNS to attract plasmatocytes to a hematopoietic niche (Makhijani et al. 2011). Expression of activated Pvr stimulates larval hemocyte proliferation, whereas dominant negative Pvr has the opposite effect (Zettervall et al. 2004). At the onset of metamorphosis, lymph glands supply large numbers of plasmatocytes to phagocytose unnecessary larval tissue. Pvr is required in the lymph gland to regulate plasmatocyte differentiation and maintain levels of mature hemocytes (Jung et al. 2005).

Pvr is additionally expressed in ovarian border cells and is required for their initial migration in the direction of *Pvf1*, expressed by the developing oocyte (McDonald et al. 2003). Pvf1 engagement by Pvr provides directionality, because Pvr inactivation results in border cell clusters with misallocated and disoriented actin protrusions (Prasad and Montell 2007; Poukkula et al. 2011). The impetus for Pvr-directed border cell migration appears collectively to be the activation of the Rac-Mbc-ELMO complex (Duchek et al. 2001; Bianco et al. 2007; Wang et al. 2010), the accumulation of cortactin and cofilin at the migratory front of the cluster (Somogyi and Rørth 2004; Zhang et al. 2011) and the down-regulation of the transcriptional repressor Aop (Schober et al. 2005).

Pvr has been implicated in the migration of imaginal cells during metamorphosis. Pvr is required for JNK-dependent thorax closure. The Rac effector Crk-Mbc-ELMO complex links Pvr to JNK in this context, similar to border cell migration (Ishimaru et al. 2004). The rotation and dorsal closure of the male genital imaginal disc also relies on Pvr/Pvf1 to activate JNK (Macias et al. 2004). Mbc-ELMO functions downstream from Pvr additionally in epithelial cells stimulated to engulf their oncogenic neighbors. In this environment, JNK is the trigger for both apoptosis in mutant cells and Pvr activation in surrounding wild-type cells (Ohsawa et al. 2011).

Pvr mutants show defects in the anterior projection of renal tubules. Like CNS remodeling, these phenotypes derive from a lack of migrating hemocytes and a consequential lack of collagen secretion/deposition, which normally facilitates Dpp presentation by dorsal epidermal and visceral mesodermal cells and directs renal tubule migration. *Pvf* expression in the renal tubules attracts and activates Pvr-expressing hemocytes (Bunt et al. 2010).

Pvf1 and Pvf3 confine Pvr activity to the apical domain of the wing imaginal disc epithelium. Unrestricted Pvr activity results in a loss of epithelial polarity, ectopic adherens junctions, elevated basolateral actin filament polymerization, and neoplastic overgrowth (Rosin et al. 2004). *Pvr* and *Pvf2* are expressed during heart metamorphosis, in cardiac valve precursors. Cardiac valves, dense accumulations of filamentous actin, are fewer following dominant-negative *Pvr* expression, whereas activated Pvr induces ectopic valve formation (Zeitouni et al. 2007). Congruent with a cardiac requirement

for *Pvr*, reduction in *Pvr* function results in aberrant embryonic/larval heart pumping (Wu and Sato 2008). However, this phenotype may reflect defective neural circuitry associated with Pvr loss (Olofsson and Page 2005) rather than defective cardiac valve development (Zeitouni et al. 2007).

Like Ryk RTKs, Pvr is required autonomously to direct salivary gland migration toward the visceral mesoderm. *Pvr* is expressed in the developing salivary gland at the incipient site of placode invagination whereas Pvf1 is abundant at the tip of the migrating gland. *Pvr* mutants, like *Pvf1* and *Pvf2* mutants, have salivary glands that curve ventrally toward the CNS (Harris et al. 2007).

Pvf2 is expressed in the adult midgut in intestinal stem cells (ISCs) and enteroblasts. Expression increases with age and in response to oxidative stress, and correlates with age and stress-dependent increases in ISC populations. Ectopic *Pvr* expression specifically in ISCs and enteroblasts causes lethality. The guts of flies that survive display elevated numbers of proliferating cells that further amplify with age. Both *Pvr* and *Pvf2* expression in ISCs stimulate their division and leads to altered differentiation—increased numbers of enteroendocrine cells at the expense of enterocytes (Choi et al. 2008). These Pvr-dependent effects rely on functional p38b ERK (Park et al. 2009).

Tie-LIKE RECEPTOR TYROSINE KINASE: ANOTHER RTK INVOLVED IN MIGRATION

Drosophila Tie-like RTK (Tie) shares ~50% identity in its TK domain with the human Tie RTK (Ito et al. 1994). Tie expression peaks at late embryonic and pupal stages (Roy et al. 2010) primarily in the hindgut, salivary gland, and trachea (Chintapalli et al. 2007). *Tie* expression is up-regulated in *Drosophila* egg chambers: specifically in border cells and centripetal cells. This up-regulation is dependent on the basic region/leucine zipper transcription factor Slbo, a C/EBP homolog. Expression of dominant-negative *Tie* exacerbates border cell migration defects resulting from dominant-negative PVR and EGFR. This indicates that Tie has a redundant role with PVR and EGFR in directing border cell cluster migration (Wang et al. 2006).

Tie likely plays a role in development of the *Drosophila* sensory system. *Tie* expression is up-regulated in *Drosophila* imaginal discs on overexpression of the Pax6 homolog Eyeless, a transcription factor directing neuronal differentiation in the retina. *Tie* is a predicted target of Eyeless, based on in silico approaches. *Tie* is expressed in the eye imaginal disc and is predicted to function early in retinal differentiation (Michaut et al. 2003; Ostrin et al. 2006).

CONCLUDING REMARKS

The breadth of scenarios wherein RTK signaling contributes to *Drosophila* development is undeniably impressive. RTKs provide a means of communication between different tissues and cell types that contributes to a robust and highly reproducible developmental program. RTKs vary dramatically in their expression with respect to cell type, ranging from ubiquitous expression, as in the case of InR for instance, to restricted expression in specific subsets of cells, as for Btl. Most interestingly, the activity of a few RTKs is exploited many times over in different developmental contexts, such as for EGFR, although the activity of other RTKs, for instance Torso and Sev, is highly specific to a few specialized functions. Remarkably, many downstream effectors are shared among different RTKs (Table 1) and their hierarchical organization is reiterated in various biological contexts. This implies that specificity in signaling output is likely rendered by a limited number of factors. For example, the insulin receptor substrate Chico is specific for InR signaling (Bohni et al. 1999), whereas the adaptor protein Shc functions downstream from Torso, EGFR, and Btl, but not Sev (Luschnig et al. 2000; Cabernard and Affolter 2005). Additionally, the context and manner in which ligands are presented to the RTK is likely to influence outcome. For instance, the overexpression of *pyr* and *ths* in combination elicits a phenotype opposite to that of individual overexpression of *pyr* or *ths* (Kadam et al. 2012). Furthermore, heparan sulfate proteoglycans are required for delivery and

stabilization of ligands with RTKs and therefore maximal activation of signaling (Nybakken and Perrimon 2001). Moreover, the competency and direction by which a cell to responds to RTK activation relies in large part on the transcription factors expressed in that particular cell type. Because of its limited genetic redundancy, *Drosophila* remains an attractive model in terms of RTK pathway component identification, and has successfully served to uncover corresponding conserved vertebrate counterparts. Components rendering fine-tuning functions in many well-characterized RTK pathways continue to be discovered. Astonishingly, relatively little is known regarding downstream signaling evoked by approximately half of all *Drosophila* RTKs. The current availability of genome-wide transgenic RNAi reagents in *Drosophila* will undoubtedly expedite further investigation of these RTKs to alleviate this knowledge gap.

ACKNOWLEDGMENTS

We thank Yanhui Hu for *Drosophila* RTK identification and Chrysoula Pitsouli and Akhila Rajan for helpful comments. R.S. is supported by the Canadian Institutes for Health Research. N.P. is a Howard Hughes Medical Institute investigator.

REFERENCES

Abrescia C, Sjostrand D, Kjaer S, Ibanez CF. 2005. *Drosophila* RET contains an active tyrosine kinase and elicits neurotrophic activities in mammalian cells. *FEBS Lett* **579:** 3789–3796.

Ahmad SM, Baker BS. 2002. Sex-specific deployment of FGF signaling in *Drosophila* recruits mesodermal cells into the male genital imaginal disc. *Cell* **109:** 651–661.

Almudi I, Stocker H, Hafen E, Corominas M, Serras F. 2009. *SOCS36E* specifically interferes with sevenless signaling during *Drosophila* eye development. *Dev Biol* **326:** 212–223.

Almudi I, Corominas M, Serras F. 2010. Competition between *SOCS36E* and Drk modulates sevenless receptor tyrosine kinase activity. *J Cell Sci* **123:** 3857–3862.

Ambrosio L, Mahowald AP, Perrimon N. 1989a. l(1)pole hole is required maternally for pattern formation in the terminal regions of the embryo. *Development* **106:** 145–158.

Ambrosio L, Mahowald AP, Perrimon N. 1989b. Requirement of the *Drosophila* raf homologue for torso function. *Nature* **342:** 288–291.

Anders J, Kjar S, Ibanez CF. 2001. Molecular modeling of the extracellular domain of the RET receptor tyrosine kinase reveals multiple cadherin-like domains and a calcium-binding site. *J Biol Chem* **276:** 35808–35817.

Arighi E, Borrello MG, Sariola H. 2005. RET tyrosine kinase signaling in development and cancer. *Cytokine Growth Factor Rev* **16:** 441–467.

Aron L, Klein P, Pham T-T, Kramer ER, Wurst W, Klein R. 2010. Pro-survival role for Parkinson's associated gene *DJ-1* revealed in trophically impaired dopaminergic neurons. *PLoS Biol* **8:** e1000349.

Astigarraga S, Grossman R, Díaz-Delfín J, Caelles C, Paroush Zae, Jiménez G. 2007. A MAPK docking site is critical for down-regulation of Capicua by Torso and EGFR RTK signaling. *EMBO J* **26:** 668–677.

Azpiazu N, Frasch M. 1993. Tinman and bagpipe: Two homeo box genes that determine cell fates in the dorsal mesoderm of *Drosophila*. *Genes Dev* **7:** 1325–1340.

Banerjee S, Gordon L, Donn TM, Berti C, Moens CB, Burden SJ, Granato M. 2011. A novel role for MuSK and non-canonical Wnt signaling during segmental neural crest cell migration. *Development* **38:** 3287–3296.

Basler K, Hafen E. 1988. Control of photoreceptor cell fate by the sevenless protein requires a functional tyrosine kinase domain. *Cell* **54:** 299–311.

Basler K, Christen B, Hafen E. 1991. Ligand-independent activation of the sevenless receptor tyrosine kinase changes the fate of cells in the developing *Drosophila* eye. *Cell* **64:** 1069–1081.

Bazigou E, Apitz H, Johansson J, Lorén CE, Hirst EMA, Chen P-L, Palmer RH, Salecker I. 2007. Anterograde Jelly belly and Alk receptor tyrosine kinase signaling mediates retinal axon targeting in *Drosophila*. *Cell* **128:** 961–975.

Behan K, Nichols C, Cheung T, Farlow A, Hogan B, Batterham P, Pollock J. 2002. Yan regulates *lozenge* during *Drosophila* eye development. *Dev Genes Evol* **212:** 267–276.

Beiman M, Shilo BZ, Volk T. 1996. Heartless, a *Drosophila* FGF receptor homolog, is essential for cell migration and establishment of several mesodermal lineages. *Genes Dev* **10:** 2993–3002.

Bellaïche Y, Bandyopadhyay R, Desplan C, Dostatni N. 1996. Neither the homeodomain nor the activation domain of Bicoid is specifically required for its down-regulation by the Torso receptor tyrosine kinase cascade. *Development* **122:** 3499–3508.

Bezakova G, Rabben I, Sefland I, Fumagalli G, Lømo T. 2001. Neural agrin controls acetylcholine receptor stability in skeletal muscle fibers. *Proc Natl Acad Sci* **98:** 9924–9929.

Bianco A, Poukkula M, Cliffe A, Mathieu J, Luque CM, Fulga TA, Rørth P. 2007. Two distinct modes of guidance signalling during collective migration of border cells. *Nature* **448:** 362–365.

Biggs WH, Zavitz KH, Dickson B, van der Straten A, Brunner D, Hafen E, Zipursky SL. 1994. The *Drosophila* rolled locus encodes a MAP kinase required in the sevenless signal transduction pathway. *EMBO J* **13:** 1628–1635.

Bodmer R. 1993. The gene tinman is required for specification of the heart and visceral muscles in *Drosophila*. *Development* **118:** 719–729.

Böhni R, Riesgo-Escovar J, Oldham S, Brogiolo W, Stocker H, Andruss BF, Beckingham K, Hafen E. 1999. Autonomous control of cell and organ size by CHICO, a *Drosophila* homolog of vertebrate IRS1–4. *Cell* **97:** 865–875.

Bolwig GM, Del Vecchio M, Hannon G, Tully T. 1995. Molecular cloning of linotte in Drosophila: A novel gene that functions in adults during associative learning. *Neuron* **15:** 829–842.

Bonkowsky JL, Thomas JB. 1999. Cell-type specific modular regulation of derailed in the *Drosophila* nervous system. *Mech Dev* **82:** 181–184.

Bossing T, Brand AH. 2002. Dephrin, a transmembrane ephrin with a unique structure, prevents interneuronal axons from exiting the *Drosophila* embryonic CNS. *Development* **129:** 4205–4218.

Boulton SJ, Brook A, Staehling-Hampton K, Heitzler P, Dyson N. 2000. A role for Ebi in neuronal cell cycle control. *EMBO J* **19:** 5376–5386.

Boyle M, Nighorn A, Thomas JB. 2006. *Drosophila* Eph receptor guides specific axon branches of mushroom body neurons. *Development* **133:** 1845–1854.

Britton JS, Edgar BA. 1998. Environmental control of the cell cycle in *Drosophila*: Nutrition activates mitotic and endoreplicative cells by distinct mechanisms. *Development* **125:** 2149–2158.

Brogiolo W, Stocker H, Ikeya T, Rintelen F, Fernandez R, Hafen E. 2001. An evolutionarily conserved function of the *Drosophila* insulin receptor and insulin-like peptides in growth control. *Curr Biol* **11:** 213–221.

Brönner G, Jäckle H. 1991. Control and function of terminal gap gene activity in the posterior pole region of the *Drosophila* embryo. *Mech Dev* **35:** 205–211.

Broughton SJ, Piper MDW, Ikeya T, Bass TM, Jacobson J, Driege Y, Martinez P, Hafen E, Withers DJ, Leevers SJ, et al. 2005. Longer lifespan, altered metabolism, and stress resistance in *Drosophila* from ablation of cells making insulin-like ligands. *Proc Natl Acad Sci* **102:** 3105–3110.

Brückner K, Kockel L, Duchek P, Luque CM, Rørth P, Perrimon N. 2004. The PDGF/VEGF receptor controls blood cell survival in *Drosophila*. *Dev Cell* **7:** 73–84.

Brunner D, Oellers N, Szabad J, Biggs WH, Zipursky SL, Hafen E. 1994. A gain-of-function mutation in *Drosophila* MAP kinase activates multiple receptor tyrosine kinase signaling pathways. *Cell* **76:** 875–888.

Bunt S, Hooley C, Hu N, Scahill C, Weavers H, Skaer H. 2010. Hemocyte-secreted type IV collagen enhances BMP signaling to guide renal tubule morphogenesis in *Drosophila*. *Dev Cell* **19:** 296–306.

Butler MJ. 2003. Discovery of genes with highly restricted expression patterns in the *Drosophila* wing disc using DNA oligonucleotide microarrays. *Development* **130:** 659–670.

Butler MJ, Jacobsen TL, Cain DM, Jarman MG, Hubank M, Whittle JR, Phillips R, Simcox A. 2003. Discovery of genes with highly restricted expression patterns in the *Drosophila* wing disc using DNA oligonucleotide microarrays. *Development* **130:** 659–670.

Cabernard C, Affolter M. 2005. Distinct roles for two receptor tyrosine kinases in epithelial branching morphogenesis in *Drosophila*. *Dev Cell* **9:** 831–842.

Cafferty P, Yu L, Rao Y. 2004. The receptor tyrosine kinase off-track is required for layer-specific neuronal connectivity in *Drosophila*. *Development* **131:** 5287–5295.

Callahan CA, Muralidhar MG, Lundgren SE, Scully AL, Thomas JB. 1995. Control of neuronal pathway selection by a *Drosophila* receptor protein-tyrosine kinase family member. *Nature* **376:** 171–174.

Callahan CA, Bonkovsky JL, Scully AL, Thomas JB. 1996. Derailed is required for muscle attachment site selection in *Drosophila*. *Development* **122:** 2761–2767.

Carmena A, Gisselbrecht S, Harrison J, Jiménez F, Michelson AM. 1998. Combinatorial signaling codes for the progressive determination of cell fates in the *Drosophila* embryonic mesoderm. *Genes Dev* **12:** 3910–3922.

Carreira VP, Mensch J, Fanara JJ. 2008. Body size in *Drosophila*: Genetic architecture, allometries and sexual dimorphism. *Heredity* **102:** 246–256.

Casali A, Casanova J. 2001. The spatial control of Torso RTK activation: A C-terminal fragment of the Trunk protein acts as a signal for Torso receptor in the *Drosophila* embryo. *Development* **128:** 1709–1715.

Casanova J, Struhl G. 1989. Localized surface activity of torso, a receptor tyrosine kinase, specifies terminal body pattern in *Drosophila*. *Genes Dev* **3:** 2025–2038.

Chang Y-Y, Juhász G, Goraksha-Hicks P, Arsham AM, Mallin DR, Muller LK, Neufeld TP. 2009. Nutrient-dependent regulation of autophagy through the target of rapamycin pathway. *Biochem Soc Trans* **37:** 232.

Charlton-Perkins M, Brown NL, Cook TA. 2011. The lens in focus: A comparison of lens development in *Drosophila* and vertebrates. *Mol Gene Genomics* **286:** 189–213.

Chell JM, Brand AH. 2010. Nutrition-responsive glia control exit of neural stem cells from quiescence. *Cell* **143:** 1161–1173.

Chen C, Jack J, Garofalo RS. 1996. The *Drosophila* insulin receptor is required for normal growth. *Endocrinology* **137:** 846–856.

Cheng LY, Bailey AP, Leevers SJ, Ragan TJ, Driscoll PC, Gould AP. 2011. Anaplastic lymphoma kinase spares organ growth during nutrient restriction in *Drosophila*. *Cell* **146:** 435–447.

Chintapalli VR, Wang J, Dow JAT. 2007. Using FlyAtlas to identify better *Drosophila melanogaster* models of human disease. *Nat Genet* **39:** 715–720.

Cho NK, Keyes L, Johnson E, Heller J, Ryner L, Karim F, Krasnow MA. 2002. Developmental control of blood cell migration by the *Drosophila* VEGF pathway. *Cell* **108:** 865–876.

Choi N-H, Kim J-G, Yang D-J, Kim Y-S, Yoo M-A. 2008. Age-related changes in *Drosophila* midgut are associated with PVF2, a PDGF/VEGF-like growth factor. *Aging Cell* **7:** 318–334.

Cinnamon E, Helman A, Ben-Haroush Schyr R, Orian A, Jimenez G, Paroush Z. 2008. Multiple RTK pathways downregulate Groucho-mediated repression in *Drosophila* embryogenesis. *Development* **135:** 829–837.

Clancy DJ, Gems D, Harshman LG, Oldham S, Stocker H, Hafen E, Leevers SJ, Partridge L. 2001. Extension of lifespan by loss of CHICO, a *Drosophila* insulin receptor substrate protein. *Science* **292:** 104–106.

Clark IBN, Muha V, Klingseisen A, Leptin M, Muller HAJ. 2011. Fibroblast growth factor signalling controls successive cell behaviors during mesoderm layer formation in *Drosophila*. *Development* **138:** 2705–2715.

Cognigni P, Bailey AP, Miguel-Aliaga I. 2011. Enteric neurons and systemic signals couple nutritional and reproductive status with intestinal homeostasis. *Cell Metab* **13:** 92–104.

Cook T, Pichaud F, Sonneville R, Papatsenko D, Desplan C. 2003. Distinction between color photoreceptor cell fates is controlled by *prospero* in *Drosophila*. *Dev Cell* **4:** 853–864.

Csiszar A, Vogelsang E, Beug H, Leptin M. 2010. A novel conserved phosphotyrosine motif in the *Drosophila* fibroblast growth factor signaling adaptor Dof with a redundant role in signal transmission. *Mol Cell Biol* **30:** 2017–2027.

Daga A, Karlovich CA, Dumstrei K, Banerjee U. 1996. Patterning of cells in the *Drosophila* eye by *lozenge*, which shares homologous domains with AML1. *Genes Dev* **10:** 1194–1205.

Dearborn R, He Q, Kunes S, Dai Y. 2002. Eph receptor tyrosine kinase-mediated formation of a topographic map in the *Drosophila* visual system. *J Neurosci* **22:** 1338–1349.

DeChiara TM, Bowen DC, Valenzuela DM, Simmons MV, Poueymirou WT, Thomas S, Kinetz E, Compton DL, Rojas E, Park JS, et al. 1996. The receptor tyrosine kinase MuSK is required for neuromuscular junction formation in vivo. *Cell* **85:** 501–512.

Demontis F, Perrimon N. 2010. FOXO/4E-BP signaling in *Drosophila* muscles regulates organism-wide proteostasis during aging. *Cell* **143:** 813–825.

DiAngelo JR, Birnbaum MJ. 2009. Regulation of fat cell mass by insulin in *Drosophila* melanogaster. *Mol Cell Biol* **29:** 6341–6352.

Dickson B, Sprenger F, Morrison D, Hafen E. 1992. Raf functions downstream of Ras1 in the sevenless signal transduction pathway. *Nature* **360:** 600–603.

Doyle HJ, Bishop JM. 1993. Torso, a receptor tyrosine kinase required for embryonic pattern formation, shares substrates with the sevenless and EGF-R pathways in *Drosophila*. *Genes Dev* **7:** 633–646.

Drummond-Barbosa D, Spradling AC. 2001. Stem cells and their progeny respond to nutritional changes during *Drosophila* oogenesis. *Dev Biol* **231:** 265–278.

Duchek P, Somogyi K, Jékely G, Beccari S, Rørth P. 2001. Guidance of cell migration by the *Drosophila* PDGF/VEGF receptor. *Cell* **107:** 17–26.

Dura JM, Taillebourg E, Préat T. 1995. The *Drosophila* learning and memory gene linotte encodes a putative receptor tyrosine kinase homologous to the human RYK gene product. *FEBS Lett* **370:** 250–254.

Dutta D, Shaw S, Maqbool T, Pandya H, VijayRaghavan K. 2005. *Drosophila* Heartless acts with Heartbroken/Dof in muscle founder differentiation. *PLoS Biol* **3:** e337.

Egger B, Leemans R, Loop T, Kammermeier L, Fan Y, Radimerski T, Strahm MC, Certa U, Reichert H. 2002. Gliogenesis in *Drosophila*: Genome-wide analysis of downstream genes of glial cells missing in the embryonic nervous system. *Development* **129:** 3295–3309.

Emori Y, Saigo K. 1993. Distinct expression of two *Drosophila* homologs of fibroblast growth factor receptors in imaginal discs. *FEBS Lett* **332:** 111–114.

Englund C, Lorén CE, Grabbe C, Varshney GK, Deleuil F, Hallberg B, Palmer RH. 2003. Jeb signals through the Alk receptor tyrosine kinase to drive visceral muscle fusion. *Nature* **425:** 512–516.

Fernandez R, Tabarini D, Azpiazu N, Frasch M, Schlessinger J. 1995. The *Drosophila* insulin receptor homolog: A gene essential for embryonic development encodes two receptor isoforms with different signaling potential. *EMBO J* **14:** 3373–3384.

Forrester WC, Dell M, Perens E, Garriga G. 1999. A *C elegans* Ror receptor tyrosine kinase regulates cell motility and asymmetric cell division. *Nature* **400:** 881–885.

Fradkin LG, van Schie M, Wouda RR, de Jong A, Kamphorst JT, Radjkoemar-Bansraj M, Noordermeer JN. 2004. The Drosophila Wnt5 protein mediates selective axon fasciculation in the embryonic central nervous system. *Dev Biol* **272:** 362–375.

Frank CA, Pielage J, Davis GW. 2009. A presynaptic homeostatic signaling system composed of the Eph receptor, Ephexin, Cdc42, and CaV2.1 calcium channels. *Neuron* **61:** 556–569.

Franzdóttir SR, Engelen D, Yuva-Aydemir Y, Schmidt I, Aho A, Klämbt C. 2009. Switch in FGF signalling initiates glial differentiation in the Drosophila eye. *Nature* **460:** 758–761.

Freeman MR, Delrow J, Kim J, Johnson E, Doe CQ. 2003. Unwrapping glial biology: Gcm target genes regulating glial development, diversification, and function. *Neuron* **38:** 567–580.

Fujimoto J, Shiota M, Iwahara T, Seki N, Satoh H, Mori S, Yamamoto T. 1996. Characterization of the transforming activity of p80, a hyperphosphorylated protein in a Ki-1 lymphoma cell line with chromosomal translocation t(2;5). *Proc Natl Acad Sci* **93:** 4181–4186.

Fung S, Wang F, Chase M, Godt D, Hartenstein V. 2007. Expression profile of the cadherin family in the developing *Drosophila* brain. *J Comp Neurol* **506:** 469–488.

Furlong EE. 2004. Integrating transcriptional and signalling networks during muscle development. *Curr Opin Genet Devt* **14:** 343–350.

Gabay L, Seger R, Shilo BZ. 1997. In situ activation pattern of *Drosophila* EGF receptor pathway during development. *Science* **277:** 1103–1106.

Gao X, Pan D. 2001. TSC1 and TSC2 tumor suppressors antagonize insulin signaling in cell growth. *Genes Dev* **15:** 1383–1392.

Gao X, Neufeld TP, Pan D. 2000. Drosophila PTEN regulates cell growth and proliferation through PI3K-dependent and -independent pathways. *Dev Biol* **221:** 404–418.

García-Alonso L, Romani S, Jiménez F. 2000. The EGF and FGF receptors mediate neuroglian function to control growth cone decisions during sensory axon guidance in *Drosophila*. *Neuron* **28:** 741–752.

Garofalo RS, Rosen OM. 1988. Tissue localization of *Drosophila melanogaster* insulin receptor transcripts during development. *Mol Cell Biol* **8:** 1638–1647.

Gaul U, Mardon G, Rubin GM. 1992. A putative Ras GTPase activating protein acts as a negative regulator of signaling

by the sevenless receptor tyrosine kinase. *Cell* **68:** 1007–1019.

Ghabrial AS, Krasnow MA. 2006. Social interactions among epithelial cells during tracheal branching morphogenesis. *Nature* **441:** 746–749.

Ghabrial AS, Levi BP, Krasnow MA. 2011. A systematic screen for tube morphogenesis and branching genes in the *Drosophila* tracheal system. *PLoS Genet* **7:** e1002087.

Gisselbrecht S, Skeath JB, Doe CQ, Michelson AM. 1996. Heartless encodes a fibroblast growth factor receptor (DFR1/DFGF-R2) involved in the directional migration of early mesodermal cells in the *Drosophila* embryo. *Genes Dev* **10:** 3003–3017.

Glazer L, Shilo BZ. 1991. The *Drosophila* FGF-R homolog is expressed in the embryonic tracheal system and appears to be required for directed tracheal cell extension. *Genes Dev* **5:** 697–705.

Gorczyca M, Augart C, Budnik V. 1993. Insulin-like receptor and insulin-like peptide are localized at neuromuscular junctions in *Drosophila*. *J Neurosci* **13:** 3692–3704.

Green JL, Inoue T, Sternberg PW. 2007. The *C. elegans* ROR receptor tyrosine kinase, CAM-1, non-autonomously inhibits the Wnt pathway. *Development* **134:** 4053–4062.

Green JL, Kuntz SG, Sternberg PW. 2008. Ror receptor tyrosine kinases: Orphans no more. *Trend Cell Biol* **18:** 536–544.

Grigorian M, Mandal L, Hakimi M, Ortiz I, Hartenstein V. 2011. The convergence of Notch and MAPK signaling specifies the blood progenitor fate in the *Drosophila* mesoderm. *Dev Biol* **353:** 105–118.

Grillenzoni N, Flandre A, Lasbleiz C, Dura JM. 2007. Respective roles of the DRL receptor and its ligand WNT5 in *Drosophila* mushroom body development. *Development* **134:** 3089–3097.

Grumolato L, Liu G, Mong P, Mudbhary R, Biswas R, Arroyave R, Vijayakumar S, Economides AN, Aaronson SA. 2010. Canonical and noncanonical Wnts use a common mechanism to activate completely unrelated coreceptors. *Genes Dev* **24:** 2517–2530.

Gryzik T, Müller HAJ. 2004. FGF8-like1 and FGF8-like2 encode putative ligands of the FGF receptor Htl and are required for mesoderm migration in the *Drosophila* gastrula. *Curr Biol* **14:** 659–667.

Guha A, Lin L, Kornberg TB. 2008. Organ renewal and cell divisions by differentiated cells in *Drosophila*. *Proc Natl Acad Sci* **105:** 10832–10836.

Hacohen N, Kramer S, Sutherland D, Hiromi Y, Krasnow MA. 1998. Sprouty encodes a novel antagonist of FGF signaling that patterns apical branching of the *Drosophila* airways. *Cell* **92:** 253–263.

Hahn M, Bishop J. 2001. Expression pattern of *Drosophila* ret suggests a common ancestral origin between the metamorphosis precursors in insect endoderm and the vertebrate enteric neurons. *Proc Natl Acad Sci* **98:** 1053–1058.

Halfon MS, Carmena A, Gisselbrecht S, Sackerson CM, Jiménez F, Baylies MK, Michelson AM. 2000. Ras pathway specificity is determined by the integration of multiple signal-activated and tissue-restricted transcription factors. *Cell* **103:** 63–74.

Harris KE, Beckendorf SK. 2007. Different Wnt signals act through the Frizzled and RYK receptors during *Drosophila* salivary gland migration. *Development* **134:** 2017–2025.

Harris KE, Schnittke N, Beckendorf SK. 2007. Two ligands signal through the *Drosophila* PDGF/VEGF receptor to ensure proper salivary gland positioning. *Mech Dev* **124:** 441–448.

Hart AC, Krämer H, Van Vactor DL, Paidhungat M, Zipursky SL. 1990. Induction of cell fate in the *Drosophila* retina: The bride of sevenless protein is predicted to contain a large extracellular domain and seven transmembrane segments. *Genes Dev* **4:** 1835–1847.

Hayashi T, Xu C, Carthew RW. 2008. Cell-type-specific transcription of *prospero* is controlled by combinatorial signaling in the *Drosophila* eye. *Development* **135:** 2787–2796.

Heino TI, Kärpänen T, Wahlström G, Pulkkinen M, Eriksson U, Alitalo K, Roos C. 2001. The *Drosophila* VEGF receptor homolog is expressed in hemocytes. *Mech Dev* **109:** 69–77.

Helman A, Cinnamon E, Mezuman S, Hayouka Z, Von Ohlen T, Orian A, Jiménez G, Paroush Zae. 2011. Phosphorylation of groucho mediates RTK feedback inhibition and prolonged pathway target gene expression. *Curr Biol* **21:** 1102–1110.

Hemphala J, Uv A, Cantera R, Bray S, Samakovlis C. 2003. Grainy head controls apical membrane growth and tube elongation in response to branchless/FGF signalling. *Development* **130:** 249–258.

Herbst R, Burden SJ. 2000. The juxtamembrane region of MuSK has a critical role in agrin-mediated signaling. *EMBO J* **19:** 67–77.

Hidalgo A, Booth GE. 2000. Glia dictate pioneer axon trajectories in the *Drosophila* embryonic CNS. *Development* **127:** 393–402.

Hikasa H, Shibata M, Hiratani I, Taira M. 2002. The *Xenopus* receptor tyrosine kinase Xror2 modulates morphogenetic movements of the axial mesoderm and neuroectoderm via Wnt signaling. *Development* **129:** 5227–5239.

Ho IS, Hannan F, Guo HF, Hakker I, Zhong Y. 2007. Distinct functional domains of neurofibromatosis type 1 regulate immediate versus long-term memory formation. *J Neurosci* **27:** 6852–6857.

Hou XS, Chou TB, Melnick MB, Perrimon N. 1995. The torso receptor tyrosine kinase can activate Raf in a Ras-independent pathway. *Cell* **81:** 63–71.

Hsu H-J, Drummond-Barbosa D. 2011. Insulin signals control the competence of the *Drosophila* female germline stem cell niche to respond to Notch ligands. *Dev Biol* **350:** 290–300.

Hsu H-J, LaFever L, Drummond-Barbosa D. 2008. Diet controls normal and tumorous germline stem cells via insulin-dependent and -independent mechanisms in *Drosophila*. *Dev Biol* **313:** 700–712.

Huang H, Potter CJ, Tao W, Li DM, Brogiolo W, Hafen E, Sun H, Xu T. 1999. PTEN affects cell size, cell proliferation and apoptosis during *Drosophila* eye development. *Development* **126:** 5365–5372.

Hurley SP, Clary DO, Copie V, Lefcort F. 2006. Anaplastic lymphoma kinase is dynamically expressed on subsets of motor neurons and in the peripheral nervous system. *J Comp Neurol* **495:** 202–212.

Ikeya T, Hayashi S. 1999. Interplay of Notch and FGF signaling restricts cell fate and MAPK activation in the *Drosophila* trachea. *Development* **126:** 4455–4463.

Ikeya T, Galic M, Belawat P, Nairz K, Hafen E. 2002. Nutrient-dependent expression of insulin-like peptides from neuroendocrine cells in the CNS contributes to growth regulation in *Drosophila*. *Curr Biol* **12:** 1293–1300.

Imam F, Sutherland D, Huang W, Krasnow MA. 1999. Stumps, a *Drosophila* gene required for fibroblast growth factor (FGF)-directed migrations of tracheal and mesodermal cells. *Genetics* **152:** 307–318.

Inaki M, Yoshikawa S, Thomas JB, Aburatani H, Nose A. 2007. Wnt4 is a local repulsive cue that determines synaptic target specificity. *Curr Biol* **17:** 1574–1579.

Ishimaru S, Ueda R, Hinohara Y, Ohtani M, Hanafusa H. 2004. PVR plays a critical role via JNK activation in thorax closure during *Drosophila* metamorphosis. *EMBO J* **23:** 3984–3994.

Ito M, Matsui T, Taniguchi T, Chihara K. 1994. Alternative splicing generates two distinct transcripts for the *Drosophila* melanogaster fibroblast growth factor receptor homolog. *Gene* **139:** 215–218.

Iwahara T, Fujimoto J, Wen D, Cupples R, Bucay N, Arakawa T, Mori S, Ratzkin B, Yamamoto T. 1997. Molecular characterization of ALK, a receptor tyrosine kinase expressed specifically in the nervous system. *Oncogene* **14:** 439–449.

Jackson Behan K, Fair J, Singh S, Bogwitz M, Perry T, Grubor V, Cunningham F, Nichols CD, Cheung TL, Batterham P, et al. 2005. Alternative splicing removes an Ets interaction domain from *lozenge* during *Drosophila* eye development. *Devt Genes Evol* **215:** 423–435.

Janody F, Sturny R, Schaeffer V, Azou Y, Dostatni N. 2001. Two distinct domains of Bicoid mediate its transcriptional down-regulation by the Torso pathway. *Development* **128:** 2281–2290.

Jarecki J, Johnson E, Krasnow MA. 1999. Oxygen regulation of airway branching in *Drosophila* is mediated by branchless FGF. *Cell* **99:** 211–220.

Jing L, Lefebvre JL, Gordon LR, Granato M. 2009. Wnt signals organize synaptic pepattern and axon guidance through the zebrafish unplugged/MuSK receptor. *Neuron* **61:** 721–733.

Johnson Hamlet MR, Perkins LA. 2001. Analysis of corkscrew signaling in the *Drosophila* epidermal growth factor receptor pathway during myogenesis. *Genetics* **159:** 1073–1087.

Jonsson M, Andersson T. 2001. Repression of Wnt-5a impairs DDR1 phosphorylation and modifies adhesion and migration of mammary cells. *J Cell Sci* **114:** 2043–2053.

Jung SH, Evans CJ, Uemura C, Banerjee U. 2005. The *Drosophila* lymph gland as a developmental model of hematopoiesis. *Development* **132:** 2521–2533.

Jünger MA, Rintelen F, Stocker H, Wasserman JD, Végh M, Radimerski T, Greenberg ME, Hafen E. 2003. The *Drosophila* forkhead transcription factor FOXO mediates the reduction in cell number associated with reduced insulin signaling. *J Biol* **2:** 20.

Kadam S, McMahon A, Tzou P, Stathopoulos A. 2009. FGF ligands in *Drosophila* have distinct activities required to support cell migration and differentiation. *Development* **136:** 739–747.

Kadam S, Ghosh S, Stathopoulos A. 2012. Synchronous and symmetric migration of *Drosophila* caudal visceral mesoderm cells requires dual input by two FGF ligands. *Development* **139:** 699–708.

Kapahi P, Zid BM, Harper T, Koslover D, Sapin V, Benzer S. 2004. Regulation of lifespan in *Drosophila* by modulation of genes in the TOR signaling pathway. *Curr Biol* **14:** 885–890.

Katso RM, Russell RB, Ganesan TS. 1999. Functional analysis of H-Ryk, an atypical member of the receptor tyrosine kinase family. *Mol Cell Biol* **19:** 6427–6440.

Keeble TR, Halford MM, Seaman C, Kee N, Macheda M, Anderson RB, Stacker SA, Cooper HM. 2006. The Wnt receptor Ryk is required for Wnt5a-mediated axon guidance on the contralateral side of the corpus callosum. *J Neurosci* **26:** 5840–5848.

Kim N, Stiegler AL, Cameron TO, Hallock PT, Gomez AM, Huang JH, Hubbard SR, Dustin ML, Burden SJ. 2008. Lrp4 is a receptor for agrin and forms a complex with MuSK. *Cell* **135:** 334–342.

Kitadate Y, Shigenobu S, Arita K, Kobayashi S. 2007. Boss/Sev signaling from germline to soma restricts germline-stem-cell-niche formation in the anterior region of *Drosophila* male gonads. *Dev Cell* **13:** 151–159.

Klambt C. 1993. The *Drosophila* gene pointed encodes two ETS-like proteins which are involved in the development of the midline glial cells. *Development* **117:** 163–176.

Klambt C, Glazer L, Shilo BZ. 1992. Breathless, a *Drosophila* FGF receptor homolog, is essential for migration of tracheal and specific midline glial cells. *Genes Dev* **6:** 1668–1678.

Klingler M, Erdélyi M, Szabad J, Nüsslein-Volhard C. 1988. Function of torso in determining the terminal anlagen of the *Drosophila* embryo. *Nature* **335:** 275–277.

Klingseisen A, Clark IBN, Gryzik T, Muller HAJ. 2009. Differential and overlapping functions of two closely related *Drosophila* FGF8-like growth factors in mesoderm development. *Development* **136:** 2393–2402.

Krämer H, Cagan RL, Zipursky SL. 1991. Interaction of bride of sevenless membrane-bound ligand and the sevenless tyrosine-kinase receptor. *Nature* **352:** 207–212.

LaFever L, Drummond-Barbosa D. 2005. Direct control of germline stem cell division and cyst growth by neural insulin in *Drosophila*. *Science* **309:** 1071–1073.

Lai ZC, Fetchko M, Li Y. 1997. Repression of *Drosophila* photoreceptor cell fate through cooperative action of two transcriptional repressors Yan and Tramtrack. *Genetics* **147:** 1131–1137.

Learte AR, Forero MG, Hidalgo A. 2008. Gliatrophic and gliatropic roles of PVF/PVR signaling during axon guidance. *Glia* **56:** 164–176.

Lee T, Hacohen N, Krasnow M, Montell DJ. 1996. Regulated breathless receptor tyrosine kinase activity required to pattern cell migration and branching in the *Drosophila* tracheal system. *Genes Dev* **10:** 2912–2921.

Lee H-H, Norris A, Weiss JB, Frasch M. 2003. Jelly belly protein activates the receptor tyrosine kinase Alk to specify visceral muscle pioneers. *Nature* **425:** 507–512.

Lemeer S, Bluwstein A, Wu Z, Leberfinger J, Müller K, Kramer K, Kuster B. 2011. Phosphotyrosine mediated protein interactions of the discoidin domain receptor 1. *J Proteomics* **75:** 3465–3477.

Li W, Skoulakis EM, Davis RL, Perrimon N. 1997. The *Drosophila* 14–3-3 protein Leonardo enhances Torso signaling through D-Raf in a Ras 1-dependent manner. *Development* **124:** 4163–4171.

Li S, Xu C, Carthew RW. 2002. Phyllopod acts as an adaptor protein to link the sina ubiquitin ligase to the substrate protein tramtrack. *Mol Cell Biol* **22:** 6854–6865.

Liao EH, Hung W, Abrams B, Zhen M. 2004. An SCF-like ubiquitin ligase complex that controls presynaptic differentiation. *Nature* **430:** 345–350.

Liebl FLW, Wu Y, Featherstone DE, Noordermeer JN, Fradkin L, Hing H. 2008. Derailed regulates development of the *Drosophila* neuromuscular junction. *Dev Neurobiol* **68:** 152–165.

Liu Y, Shi J, Lu C-C, Wang Z-B, Lyuksyutova AI, Song X, Zou Y. 2005. Ryk-mediated Wnt repulsion regulates posterior-directed growth of corticospinal tract. *Nat Neurosci* **8:** 1151–1159.

Liu X, Krause WC, Davis RL. 2007. GABAA receptor RDL inhibits *Drosophila* olfactory associative learning. *Neuron* **56:** 1090–1102.

Lorén CE, Englund C, Grabbe C, Hallberg B, Hunter T, Palmer RH. 2003. A crucial role for the Anaplastic lymphoma kinase receptor tyrosine kinase in gut development in *Drosophila* melanogaster. *EMBO Rep* **4:** 781–786.

Lovegrove B, Simões S, Rivas ML, Sotillos S, Johnson K, Knust E, Jacinto A, Hombría JC-G. 2006. Coordinated control of cell adhesion, polarity, and cytoskeleton underlies Hox-induced organogenesis in *Drosophila*. *Curr Biol* **16:** 2206–2216.

Lu X, Chou TB, Williams NG, Roberts T, Perrimon N. 1993. Control of cell fate determination by p21ras/Ras1, an essential component of torso signaling in *Drosophila*. *Genes Dev* **7:** 621–632.

Lu X, Melnick MB, Hsu JC, Perrimon N. 1994. Genetic and molecular analyses of mutations involved in *Drosophila* raf signal transduction. *EMBO J* **13:** 2592–2599.

Lu W, Yamamoto V, Ortega B, Baltimore D. 2004. Mammalian Ryk is a wnt coreceptor required for stimulation of neurite outgrowth. *Cell* **119:** 97–108.

Luschnig S, Krauss J, Bohmann K, Desjeux I, Nüsslein-Volhard C. 2000. The *Drosophila* SHC adaptor protein is required for signaling by a subset of receptor tyrosine kinases. *Mol Cell* **5:** 231–241.

Mace KA, Pearson JC, McGinnis W. 2005. An epidermal barrier wound repair pathway in *Drosophila* is mediated by grainy head. *Science* **308:** 381–385.

Macias A, Romero NM, Martin F, Suarez L, Rosa AL, Morata G. 2004. PVF1/PVR signaling and apoptosis promotes the rotation and dorsal closure of the *Drosophila* male terminalia. *Int J Dev Biol* **48:** 1087–1094.

Makhijani K, Alexander B, Tanaka T, Rulifson E, Brückner K. 2011. The peripheral nervous system supports blood cell homing and survival in the *Drosophila* larva. *Development* **138:** 5379–5391.

Mandal L, Dumstrei K, Hartenstein V. 2004. Role of FGFR signaling in the morphogenesis of the *Drosophila* visceral musculature. *Dev Dyn* **231:** 342–348.

Maqbool T, Soler C, Jagla T, Daczewska M, Lodha N, Palliyil S, VijayRaghavan K, Jagla K. 2006. Shaping leg muscles in *Drosophila*: Role of ladybird, a conserved regulator of appendicular myogenesis. *PLoS ONE* **1:** e122.

Martin DN, Balgley B, Dutta S, Chen J, Rudnick P, Cranford J, Kantartzis S, DeVoe DL, Lee C, Baehrecke EH. 2007. Proteomic analysis of steroid-triggered autophagic programmed cell death during *Drosophila* development. *Cell Death Differ* **14:** 916–923.

Martin-Pena A, Acebes A, Rodriguez JR, Sorribes A, de Polavieja GG, Fernandez-Funez P, Ferrus A. 2006. Age-independent synaptogenesis by phosphoinositide 3 kinase. *J Neurosci* **26:** 10199–10208.

Maurel-Zaffran C, Pradel J, Graba Y. 2010. Reiterative use of signalling pathways controls multiple cellular events during *Drosophila* posterior spiracle organogenesis. *Dev Biol* **343:** 18–27.

McBrayer Z, Ono H, Shimell M, Parvy J-P, Beckstead RB, Warren JT, Thummel CS, Dauphin-Villemant C, Gilbert LI, O'Connor MB. 2007. Prothoracicotropic hormone regulates developmental timing and body size in *Drosophila*. *Dev Cell* **13:** 857–871.

McDonald JA, Pinheiro EM, Montell DJ. 2003. PVF1, a PDGF/VEGF homolog, is sufficient to guide border cells and interacts genetically with Taiman. *Development* **130:** 3469–3478.

McLeod CJ, Wang L, Wong C, Jones DL. 2010. Stem cell dynamics in response to nutrient availability. *Curr Biol* **20:** 2100–2105.

McMahon A, Supatto W, Fraser SE, Stathopoulos A. 2008. Dynamic analyses of *Drosophila* gastrulation provide insights into collective cell migration. *Science* **322:** 1546–1550.

McMahon A, Reeves GT, Supatto W, Stathopoulos A. 2010. Mesoderm migration in *Drosophila* is a multi-step process requiring FGF signaling and integrin activity. *Development* **137:** 2167–2175.

Michaut L, Flister S, Neeb M, White KP, Certa U, Gehring WJ. 2003. Analysis of the eye developmental pathway in *Drosophila* using DNA microarrays. *Proc Natl Acad Sci* **100:** 4024–4029.

Michelson AM, Gisselbrecht S, Buff E, Skeath JB. 1998a. Heartbroken is a specific downstream mediator of FGF receptor signalling in *Drosophila*. *Development* **125:** 4379–4389.

Michelson AM, Gisselbrecht S, Zhou Y, Baek KH, Buff EM. 1998b. Dual functions of the heartless fibroblast growth factor receptor in development of the *Drosophila* embryonic mesoderm. *Dev Genet* **22:** 212–229.

Miguel-Aliaga I, Thor S, Gould AP. 2008. Postmitotic specification of *Drosophila* insulinergic neurons from pioneer neurons. *PLoS Biol* **6:** e58.

Mikels AJ, Nusse R. 2006. Purified Wnt5a protein activates or inhibits β-catenin–TCF signaling depending on receptor context. *PLoS Biol* **4:** e115.

Min K-J, Yamamoto R, Buch S, Pankratz M, Tatar M. 2008. Drosophila lifespan control by dietary restriction independent of insulin-like signaling. *Aging Cell* **7:** 199–206.

Montagne J, Stewart MJ, Stocker H, Hafen E, Kozma SC, Thomas G. 1999. *Drosophila* S6 kinase: A regulator of cell size. *Science* **285:** 2126–2129.

Moore LA, Broihier HT, Van Doren M, Lunsford LB, Lehmann R. 1998. Identification of genes controlling germ cell migration and embryonic gonad formation in *Drosophila*. *Development* **125:** 667–678.

Moran E, Jimenez G. 2006. The tailless nuclear receptor acts as a dedicated repressor in the early *Drosophila* embryo. *Mol Cell Biol* **26:** 3446–3454.

Moreau-Fauvarque C, Taillebourg E, Boissoneau E, Mesnard J, Dura JM. 1998. The receptor tyrosine kinase gene linotte is required for neuronal pathway selection in the *Drosophila* mushroom bodies. *Mech Dev* **78:** 47–61.

Mukherjee T, Choi I, Banerjee U, Lipshitz HD. 2012. Genetic analysis of fibroblast growth factor signaling in the *Drosophila* eye. *G3 (Bethesda)* **2:** 23–28.

Murray MJ, Saint R. 2007. Photoactivatable GFP resolves *Drosophila* mesoderm migration behavior. *Development* **134:** 3975–3983.

Nasiadka A, Dietrich BH, Krause HM. 2002. Anterior–posterior patterning in the *Drosophila* embryo. In *Advances in developmental biology and biochemistry* (ed. DePamphilis M), pp. 1–50. Elsevier Science, Amsterdam.

Nicola M, Lasbleiz C, Dura J-M. 2003. Gain-of-function screen identifies a role of the Src64 oncogene in *Drosophila* mushroom body development. *J Neurobiol* **57:** 291–302.

Nüsslein-Volhard C, Frohnhöfer HG, Lehmann R. 1987. Determination of anteroposterior polarity in *Drosophila*. *Science* **238:** 1675–1681.

Oates AC, Bonkovsky JL, Irvine DV, Kelly LE, Thomas JB, Wilks AF. 1998. Embryonic expression and activity of doughnut, a second RYK homolog in *Drosophila*. *Mech Dev* **78:** 165–169.

Ohsawa S, Sugimura K, Takino K, Xu T, Miyawaki A, Igaki T. 2011. Elimination of oncogenic neighbors by JNK-mediated engulfment in *Drosophila*. *Dev Cell* **20:** 315–328.

Ohshiro T, Emori Y, Saigo K. 2002. Ligand-dependent activation of breathless FGF receptor gene in *Drosophila* developing trachea. *Mech Dev* **114:** 3–11.

Oishi I, Sugiyama S, Liu ZJ, Yamamura H, Nishida Y, Minami Y. 1997. A novel *Drosophila* receptor tyrosine kinase expressed specifically in the nervous system. Unique structural features and implication in developmental signaling. *J Biol Chem* **272:** 11916–11923.

Oishi I, Suzuki H, Onishi N, Takada R, Kani S, Ohkawara B, Koshida I, Suzuki K, Yamada G, Schwabe GC, et al. 2003. The receptor tyrosine kinase Ror2 is involved in non-canonical Wnt5a/JNK signalling pathway. *Genes Cells* **8:** 645–654.

Okamoto N, Yamanaka N, Yagi Y, Nishida Y, Kataoka H, Connor MBO, Mizoguchi A. 2009. A fat body-derived IGF-like peptide regulates postfeeding growth in *Drosophila*. *Dev Cell* **17:** 885–891.

Oldham S, Montagne J, Radimerski T, Thomas G, Hafen E. 2000. Genetic and biochemical characterization of dTOR, the *Drosophila* homolog of the target of rapamycin. *Genes Dev* **14:** 2689–2694.

Oldham S, Stocker H, Laffargue M, Wittwer F, Wymann M, Hafen E. 2002. The *Drosophila* insulin/IGF receptor controls growth and size by modulating PtdInsP_3 levels. *Development* **129:** 4103–4109.

Olivier JP, Raabe T, Henkemeyer M, Dickson B, Mbamalu G, Margolis B, Schlessinger J, Hafen E, Pawson T. 1993. A *Drosophila* SH2-SH3 adaptor protein implicated in coupling the sevenless tyrosine kinase to an activator of Ras guanine nucleotide exchange, Sos. *Cell* **73:** 179–191.

Olofsson B, Page DT. 2005. Condensation of the central nervous system in embryonic *Drosophila* is inhibited by blocking hemocyte migration or neural activity. *Dev Biol* **279:** 233–243.

O'Neill EM, Rebay I, Tjian R, Rubin GM. 1994. The activities of two Ets-related transcription factors required for *Drosophila* eye development are modulated by the Ras/MAPK pathway. *Cell* **78:** 137–147.

Ostrin EJ, Li Y, Hoffman K, Liu J, Wang K, Zhang L, Mardon G, Chen R. 2006. Genome-wide identification of direct targets of the *Drosophila* retinal determination protein Eyeless. *Genome Res* **16:** 466–476.

Paganoni S, Ferreira A. 2005. Neurite extension in central neurons: A novel role for the receptor tyrosine kinases Ror1 and Ror2. *J Cell Sci* **118:** 433–446.

Paganoni S, Bernstein J, Ferreira A. 2010. Ror1–Ror2 complexes modulate synapse formation in hippocampal neurons. *Neuroscience* **165:** 1261–1274.

Park J-S, Kim Y-S, Yoo M-A. 2009. The role of p38b MAPK in age-related modulation of intestinal stem cell proliferation and differentiation in *Drosophila*. *Aging* **1:** 637–651.

Peradziryi H, Kaplan NA, Podleschny M, Liu X, Wehner P, Borchers A, Tolwinski NS. 2011. PTK7/Otk interacts with Wnts and inhibits canonical Wnt signalling. *EMBO J* **30:** 3729–3740.

Perkins LA, Larsen I, Perrimon N. 1992. *corkscrew* encodes a putative protein tyrosine phosphatase that functions to transduce the terminal signal from the receptor tyrosine kinase torso. *Cell* **70:** 225–236.

Perrimon N, McMahon AP. 1999. Negative feedback mechanisms and their roles during pattern formation. *Cell* **97:** 13–16.

Perrimon N, Perkins LA. 1997. There must be 50 ways to rule the signal: The case of the *Drosophila* EGF receptor. *Cell* **89:** 13–16.

Perrimon N, Mohler D, Engstrom L, Mahowald AP. 1986. X-linked female-sterile loci in *Drosophila* melanogaster. *Genetics* **113:** 695–712.

Perrimon N, Lu X, Hou XS, Hsu JC, Melnick MB, Chou TB, Perkins LA. 1995. Dissection of the torso signal transduction pathway in *Drosophila*. *Mol Reprod Dev* **42:** 515–522.

Petit V, Nussbaumer U, Dossenbach C, Affolter M. 2004. Downstream-of-FGFR is a fibroblast growth factor-specific scaffolding protein and recruits Corkscrew upon receptor activation. *Mol Cell Biol* **24:** 3769–3781.

Petruzzelli L, Herrera R, Arenas-Garcia R, Fernandez R, Birnbaum MJ, Rosen OM. 1986. Isolation of a *Drosophila* genomic sequence homologous to the kinase domain of the human insulin receptor and detection of the phosphorylated *Drosophila* receptor with an anti-peptide antibody. *Proc Natl Acad Sci* **83:** 4710–4714.

Pignoni F, Baldarelli RM, Steingrímsson E, Diaz RJ, Patapoutian A, Merriam JR, Lengyel JA. 1990. The *Drosophila* gene tailless is expressed at the embryonic termini and is a member of the steroid receptor superfamily. *Cell* **62:** 151–163.

Pignoni F, Steingrímsson E, Lengyel JA. 1992. Bicoid and the terminal system activate tailless expression in the early *Drosophila* embryo. *Development* **115:** 239–251.

Pitsouli C, Perrimon N. 2010. Embryonic multipotent progenitors remodel the *Drosophila* airways during metamorphosis. *Development* **137:** 3615–3624.

Potter CJ, Huang H, Xu T. 2001. *Drosophila* Tsc1 functions with Tsc2 to antagonize insulin signaling in regulating cell growth, cell proliferation, and organ size. *Cell* **105:** 357–368.

Poukkula M, Cliffe A, Changede R, Rørth P. 2011. Cell behaviors regulated by guidance cues in collective migration of border cells. *J Cell Biol* **192:** 513–524.

Prasad M, Montell DJ. 2007. Cellular and molecular mechanisms of border cell migration analyzed using time-lapse live-cell imaging. *Dev Cell* **12:** 997–1005.

Pulido D, Campuzano S, Koda T, Modolell J, Barbacid M. 1992. Dtrk, a *Drosophila* gene related to the trk family of neurotrophin receptors, encodes a novel class of neural cell adhesion molecule. *EMBO J* **11:** 391–404.

Raabe T, Riesgo-Escovar J, Liu X, Bausenwein BS, Deak P, Maröy P, Hafen E. 1996. DOS, a novel pleckstrin homology domain-containing protein required for signal transduction between sevenless and Ras1 in *Drosophila*. *Cell* **85:** 911–920.

Read RD, Goodfellow PJ, Mardis ER, Novak N, Armstrong JR, Cagan RL. 2005. A *Drosophila* model of multiple endocrine neoplasia type 2. *Genetics* **171:** 1057–1081.

Rebay I, Rubin GM. 1995. Yan functions as a general inhibitor of differentiation and is negatively regulated by activation of the Ras1/MAPK pathway. *Cell* **81:** 857–866.

Reichman-Fried M, Shilo BZ. 1995. Breathless, a *Drosophila* FGF receptor homolog, is required for the onset of tracheal cell migration and tracheole formation. *Mech Dev* **52:** 265–273.

Reiner DJ, Ailion M, Thomas JH, Meyer BJ. 2008. *C elegans* anaplastic lymphoma kinase ortholog SCD-2 controls dauer formation by modulating TGF-β signaling. *Curr Biol* **18:** 1101–1109.

Reinke R, Zipursky SL. 1988. Cell–cell interaction in the *Drosophila* retina: The bride of sevenless gene is required in photoreceptor cell R8 for R7 cell development. *Cell* **55:** 321–330.

Rewitz KF, Yamanaka N, Gilbert LI, O'Connor MB. 2009. The insect neuropeptide PTTH activates receptor tyrosine kinase torso to initiate metamorphosis. *Science* **326:** 1403–1405.

Ribeiro C, Ebner A, Affolter M. 2002. In vivo imaging reveals different cellular functions for FGF and Dpp signaling in tracheal branching morphogenesis. *Dev Cell* **2:** 677–683.

Rintelen F, Stocker H, Thomas G, Hafen E. 2001. PDK1 regulates growth through Akt and S6K in *Drosophila*. *Proc Natl Acad Sci* **98:** 15020–15025.

Rogge RD, Karlovich CA, Banerjee U. 1991. Genetic dissection of a neurodevelopmental pathway: Son of sevenless functions downstream of the sevenless and EGF receptor tyrosine kinases. *Cell* **64:** 39–48.

Rogge R, Cagan R, Majumdar A, Dulaney T, Banerjee U. 1992. Neuronal development in the *Drosophila* retina: The sextra gene defines an inhibitory component in the developmental pathway of R7 photoreceptor cells. *Proc Natl Acad Sci* **89:** 5271–5275.

Rohrbough J, Broadie K. 2010. Anterograde Jelly belly ligand to Alk receptor signaling at developing synapses is regulated by Mind the gap. *Development* **137:** 3523–3533.

Ronchi E, Treisman J, Dostatni N, Struhl G, Desplan C. 1993. Down-regulation of the *Drosophila* morphogen bicoid by the torso receptor-mediated signal transduction cascade. *Cell* **74:** 347–355.

Rosin D, Schejter E, Volk T, Shilo BZ. 2004. Apical accumulation of the *Drosophila* PDGF/VEGF receptor ligands provides a mechanism for triggering localized actin polymerization. *Development* **131:** 1939–1948.

Roy S, Ernst J, Kharchenko PV, Kheradpour P, Negre N, Eaton ML, Landolin JM, Bristow CA, Ma L, Lin MF, et al. 2010. Identification of functional elements and regulatory circuits by *Drosophila* modENCODE. *Science* **330:** 1787–1797.

Rulifson EJ, Kim SK, Nusse R. 2002. Ablation of insulin-producing neurons in flies: Growth and diabetic phenotypes. *Science* **296:** 1118–1120.

Sakurai M, Aoki T, Yoshikawa S, Santschi LA, Saito H, Endo K, Ishikawa K, Kimura Ki, Ito K, Thomas JB, et al. 2009. Differentially expressed Drl and Drl-2 play opposing roles in Wnt5 signaling during Drosophila olfactory system development. *J Neurosci* **29:** 4972–4980.

Saldanha J, Singh J, Mahadevan D. 1998. Identification of a Frizzled-like cysteine rich domain in the extracellular region of developmental receptor tyrosine kinases. *Protein Sci* **7:** 1632–1635.

Samakovlis C, Hacohen N, Manning G, Sutherland DC, Guillemin K, Krasnow MA. 1996. Development of the *Drosophila* tracheal system occurs by a series of morphologically distinct but genetically coupled branching events. *Development* **122:** 1395–1407.

Sato M, Kornberg TB. 2002. FGF is an essential mitogen and chemoattractant for the air sacs of the Drosophila tracheal system. *Dev Cell* **3:** 195–207.

Sato M, Kitada Y, Tabata T. 2008. Larval cells become imaginal cells under the control of homothorax prior to metamorphosis in the *Drosophila* tracheal system. *Dev Biol* **318:** 247–257.

Savant-Bhonsale S, Friese M, McCoon P, Montell DJ. 1999. A *Drosophila* derailed homolog, doughnut, expressed in invaginating cells during embryogenesis. *Gene* **231:** 155–161.

Schober M, Rebay I, Perrimon N. 2005. Function of the ETS transcription factor Yan in border cell migration. *Development* **132:** 3493–3504.

Schulz RA, Gajewski K. 1999. Ventral neuroblasts and the heartless FGF receptor are required for muscle founder cell specification in *Drosophila*. *Oncogene* **18:** 6818–6823.

Schumacher S, Gryzik T, Tannebaum S, Muller HA. 2004. The RhoGEF Pebble is required for cell shape changes during cell migration triggered by the *Drosophila* FGF receptor heartless. *Development* **131:** 2631–2640.

Schupbach T, Wieschaus E. 1986. Germline autonomy of maternal-effect mutations altering the embryonic body pattern of *Drosophila*. *Dev Biol* **113:** 443–448.

Schupbach T, Wieschaus E. 1989. Female sterile mutations on the second chromosome of *Drosophila* melanogaster. I. Maternal effect mutations. *Genetics* **121:** 101–117.

Scully AL, McKeown M, Thomas JB. 1999. Isolation and characterization of Dek, a *Drosophila* eph receptor protein tyrosine kinase. *Mol Cell Neurosci* **13:** 337–347.

Sears HC, Kennedy CJ, Garrity PA. 2003. Macrophage-mediated corpse engulfment is required for normal *Drosophila* CNS morphogenesis. *Development* **130:** 3557–3565.

Shcherbata HR, Yatsenko AS, Patterson L, Sood VD, Nudel U, Yaffe D, Baker D, Ruohola-Baker H. 2007. Dissecting muscle and neuronal disorders in a *Drosophila* model of muscular dystrophy. *EMBO J* **26:** 481–493.

Shilo B. 2003. Signaling by the *Drosophila* epidermal growth factor receptor pathway during development. *Exp Cell Res* **284:** 140–149.

Shilo BZ. 2005. Regulating the dynamics of EGF receptor signaling in space and time. *Development* **132:** 4017–4027.

Shirinian M, Varshney G, Lorén CE, Grabbe C, Palmer RH. 2007. *Drosophila* anaplastic lymphoma kinase regulates Dpp signalling in the developing embryonic gut. *Differentiation* **75:** 418–426.

Shishido E, Higashijima S, Emori Y, Saigo K. 1993. Two FGF-receptor homologues of *Drosophila*: One is expressed in mesodermal primordium in early embryos. *Development* **117:** 751–761.

Shishido E, Ono N, Kojima T, Saigo K. 1997. Requirements of DFR1/heartless, a mesoderm-specific *Drosophila* FGF-receptor, for the formation of heart, visceral and somatic muscles, and ensheathing of longitudinal axon tracts in CNS. *Development* **124:** 2119–2128.

Shrivastava A, Radziejewski C, Campbell E, Kovac L, McGlynn M, Ryan TE, Davis S, Goldfarb MP, Glass DJ, Lemke G, et al. 1997. An orphan receptor tyrosine kinase family whose members serve as nonintegrin collagen receptors. *Mol Cell* **1:** 25–34.

Siddall NA, Hime GR, Pollock JA, Batterham P. 2009. Ttk69-dependent repression of *lozenge* prevents the ectopic development of R7 cells in the *Drosophila* larval eye disc. *BMC Dev Biol* **9:** 64.

Siegrist SE, Haque NS, Chen C-H, Hay BA, Hariharan IK. 2010. Inactivation of both foxo and reaper promotes long-term adult neurogenesis in *Drosophila*. *Curr Biol* **20:** 643–648.

Simon MA, Bowtell DD, Dodson GS, Laverty TR, Rubin GM. 1991. Ras1 and a putative guanine nucleotide exchange factor perform crucial steps in signaling by the sevenless protein tyrosine kinase. *Cell* **67:** 701–716.

Simon MA, Dodson GS, Rubin GM. 1993. An SH3-SH2-SH3 protein is required for p21Ras1 activation and binds to sevenless and Sos proteins in vitro. *Cell* **73:** 169–177.

Simon AF, Boquet I, Synguélakis M, Préat T. 1998. The *Drosophila* putative kinase linotte (derailed) prevents central brain axons from converging on a newly described interhemispheric ring. *Mech Dev* **76:** 45–55.

Singh AP, VijayRaghavan K, Rodrigues V. 2010. Dendritic refinement of an identified neuron in the *Drosophila* CNS is regulated by neuronal activity and Wnt signaling. *Development* **137:** 1351–1360.

Slaidina M, Delanoue R, Gronke S, Partridge L, Léopold P. 2009. A *Drosophila* insulin-like peptide promotes growth during nonfeeding states. *Dev Cell* **17:** 874–884.

Somogyi K, Rørth P. 2004. Cortactin modulates cell migration and ring canal morphogenesis during *Drosophila* oogenesis. *Mech Dev* **121:** 57–64.

Song J, Wu L, Chen Z, Kohanski RA, Pick L. 2003. Axons guided by insulin receptor in *Drosophila* visual system. *Science* **300:** 502–505.

Sossin WS. 2006. Tracing the evolution and function of the Trk superfamily of receptor tyrosine kinases. *Brain Behav Evol* **68:** 145–156.

Sousa-Nunes R, Yee LL, Gould AP. 2011. Fat cells reactivate quiescent neuroblasts via TOR and glial insulin relays in *Drosophila*. *Nature* **471:** 508–512.

Sprenger F, Nüsslein-Volhard C. 1992. Torso receptor activity is regulated by a diffusible ligand produced at the extracellular terminal regions of the *Drosophila* egg. *Cell* **71:** 987–1001.

Sprenger F, Stevens LM, Nüsslein-Volhard C. 1989. The *Drosophila* gene torso encodes a putative receptor tyrosine kinase. *Nature* **338:** 478–483.

Sprenger F, Trosclair MM, Morrison DK. 1993. Biochemical analysis of torso and D-raf during *Drosophila* embryogenesis: Implications for terminal signal transduction. *Mol Cell Biol* **13:** 1163–1172.

Srahna M, Leyssen M, Choi CM, Fradkin LG, Noordermeer JN, Hassan BA. 2006. A signaling network for patterning of neuronal connectivity in the *Drosophila* brain. *PLoS Biol* **4:** e348.

Stathopoulos A, Tam B, Ronshaugen M, Frasch M, Levine M. 2004. pyramus and thisbe: FGF genes that pattern the mesoderm of *Drosophila* embryos. *Genes Dev* **18:** 687–699.

Steingrímsson E, Pignoni F, Liaw GJ, Lengyel JA. 1991. Dual role of the *Drosophila* pattern gene tailless in embryonic termini. *Science* **254:** 418–421.

Stevens LM, Frohnhöfer HG, Klingler M, Nüsslein-Volhard C. 1990. Localized requirement for torso-like expression in follicle cells for development of terminal anlagen of the *Drosophila* embryo. *Nature* **346:** 660–663.

Strecker TR, Halsell SR, Fisher WW, Lipshitz HD. 1989. Reciprocal effects of hyper- and hypoactivity mutations in the *Drosophila* pattern gene torso. *Science* **243:** 1062–1066.

Stute C, Schimmelpfeng K, Renkawitz-Pohl R, Palmer RH, Holz A. 2004. Myoblast determination in the somatic and visceral mesoderm depends on Notch signalling as well as on milliways (mili(Alk)) as receptor for Jeb signalling. *Development* **131:** 743–754.

Sugaya R, Ishimaru S, Hosoya T, Saigo K, Emori Y. 1994. A *Drosophila* homolog of human proto-oncogene ret transiently expressed in embryonic neuronal precursor cells including neuroblasts and CNS cells. *Mech Dev* **45:** 139–145.

Sutherland D, Samakovlis C, Krasnow MA. 1996. branchless encodes a *Drosophila* FGF homolog that controls tracheal

cell migration and the pattern of branching. *Cell* **87:** 1091–1101.

Szabad J, Erdelyi M, Hoffmann G, Szidonya J, Wright TR. 1989. Isolation and characterization of dominant female sterile mutations of *Drosophila* melanogaster. II. Mutations on the second chromosome. *Genetics* **122:** 823–835.

Tang AH, Neufeld TP, Kwan E, Rubin GM. 1997. PHYL acts to down-regulate TTK88, a transcriptional repressor of neuronal cell fates, by a SINA-dependent mechanism. *Cell* **90:** 459–467.

Tatar M, Kopelman A, Epstein D, Tu MP, Yin CM, Garofalo RS. 2001. A mutant *Drosophila* insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science* **292:** 107–110.

Tepass U, Fessler LI, Aziz A, Hartenstein V. 1994. Embryonic origin of hemocytes and their relationship to cell death in *Drosophila*. *Development* **120:** 1829–1837.

Tepass U, Truong K, Godt D, Ikura M, Peifer M. 2000. Cadherins in embryonic and neural morphogenesis. *Nat Rev Mol Cell Biol* **1:** 91–100.

Therrien M, Chang HC, Solomon NM, Karim FD, Wassarman DA, Rubin GM. 1995. KSR, a novel protein kinase required for RAS signal transduction. *Cell* **83:** 879–888.

Tomlinson A, Ready DF. 1986. Sevenless: A cell-specific homeotic mutation of the *Drosophila* eye. *Science* **231:** 400–402.

Tomlinson A, Ready DF. 1987. Cell fate in the *Drosophila* ommatidium. *Dev Biol* **123:** 264–275.

Tomlinson A, Bowtell DD, Hafen E, Rubin GM. 1987. Localization of the sevenless protein, a putative receptor for positional information, in the eye imaginal disc of *Drosophila*. *Cell* **51:** 143–150.

Tootle TL, Lee PS, Rebay I. 2003. CRM1-mediated nuclear export and regulated activity of the receptor tyrosine kinase antagonist YAN require specific interactions with MAE. *Development* **130:** 845–857.

Tsuda L, Inoue YH, Yoo MA, Mizuno M, Hata M, Lim YM, Adachi-Yamada T, Ryo H, Masamune Y, Nishida Y. 1993. A protein kinase similar to MAP kinase activator acts downstream of the raf kinase in *Drosophila*. *Cell* **72:** 407–414.

Tsuda H, Han SM, Yang Y, Tong C, Lin YQ, Mohan K, Haueter C, Zoghbi A, Harati Y, Kwan J, et al. 2008. The amyotrophic lateral sclerosis 8 Protein VAPB is cleaved, secreted, and acts as a ligand for Eph receptors. *Cell* **133:** 963–977.

Tu M-P, Tatar M. 2003. Juvenile diet restriction and the aging and reproduction of adult *Drosophila* melanogaster. *Aging Cell* **2:** 327–333.

Ueishi S, Shimizu H, Inoue YH. 2009. Male germline stem cell division and spermatocyte growth require insulin signaling in *Drosophila*. *Cell Struct Funct* **34:** 61–69.

Varshney GK, Palmer RH. 2006. The bHLH transcription factor Hand is regulated by Alk in the *Drosophila* embryonic gut. *Biochem Biophys Res Commun* **351:** 839–846.

Veenstra JA, Agricola H-J, Sellami A. 2008. Regulatory peptides in fruit fly midgut. *Cell Tissue Res* **334:** 499–516.

Verdu J, Buratovich MA, Wilder EL, Birnbaum MJ. 1999. Cell-autonomous regulation of cell and organ growth in *Drosophila* by Akt/PKB. *Nat Cell Biol* **1:** 500–506.

Vernersson E, Khoo NKS, Henriksson ML, Roos G, Palmer RH, Hallberg B. 2006. Characterization of the expression of the ALK receptor tyrosine kinase in mice. *Gene Expr Patterns* **6:** 448–461.

Vincent S, Wilson R, Coelho C, Affolter M, Leptin M. 1998. The *Drosophila* protein Dof is specifically required for FGF signaling. *Mol Cell* **2:** 515–525.

Voas MG, Rebay I. 2003. Signal integration during development: Insights from the *Drosophila* eye. *Dev Dyn* **229:** 162–175.

Vogel W, Gish GD, Alves F, Pawson T. 1997. The discoidin domain receptor tyrosine kinases are activated by collagen. *Mol Cell* **1:** 13–23.

Vogel WF, Abdulhussein R, Ford CE. 2006. Sensing extracellular matrix: An update on discoidin domain receptor function. *Cell Signal* **18:** 1108–1116.

Walker JA, Tchoudakova AV, McKenney PT, Brill S, Wu D, Cowley GS, Hariharan IK, Bernards A. 2006. Reduced growth of *Drosophila* neurofibromatosis 1 mutants reflects a non-cell-autonomous requirement for GTPase-activating protein activity in larval neurons. *Genes Dev* **20:** 3311–3323.

Wang X, Bo J, Bridges T, Dugan KD, Pan T-c, Chodosh LA, Montell DJ. 2006. Analysis of cell migration using whole-genome expression profiling of migratory cells in the *Drosophila* ovary. *Dev Cell* **10:** 483–495.

Wang S, Tsarouhas V, Xylourgidis N, Sabri N, Tiklová K, Nautiyal N, Gallio M, Samakovlis C. 2009. The tyrosine kinase Stitcher activates Grainy head and epidermal wound healing in *Drosophila*. *Nature* **11:** 890–895.

Wang X, He L, Wu YI, Hahn KM, Montell DJ. 2010. Light-mediated activation reveals a key role for Rac in collective guidance of cell movement in vivo. *Nature* **12:** 591–597.

Weaver M, Krasnow MA. 2008. Dual origin of tissue-specific progenitor cells in *Drosophila* tracheal remodeling. *Science* **321:** 1496–1499.

Weigel D, Jürgens G, Klingler M, Jäckle H. 1990. Two gap genes mediate maternal terminal pattern information in *Drosophila*. *Science* **248:** 495–498.

Weinkove D, Neufeld TP, Twardzik T, Waterfield MD, Leevers SJ. 1999. Regulation of imaginal disc cell size, cell number and organ size by *Drosophila* class I(A) phosphoinositide 3-kinase and its adaptor. *Curr Biol* **9:** 1019–1029.

Weiss JB, Suyama KL, Lee HH, Scott MP. 2001. Jelly belly: A *Drosophila* LDL receptor repeat-containing signal required for mesoderm migration and differentiation. *Cell* **107:** 387–398.

Wilson R. 2005. FGF signalling and the mechanism of mesoderm spreading in *Drosophila* embryos. *Development* **132:** 491–501.

Wilson C, Goberdhan DC, Steller H. 1993. Dror, a potential neurotrophic receptor gene, encodes a *Drosophila* homolog of the vertebrate Ror family of Trk-related receptor tyrosine kinases. *Proc Natl Acad Sci* **90:** 7109–7113.

Wilson R, Battersby A, Csiszar A, Vogelsang E, Leptin M. 2004. A functional domain of Dof that is required for fibroblast growth factor signaling. *Mol Cell Biol* **24:** 2263–2276.

Wilson R, Vogelsang E, Leptin M. 2005. FGF signalling and the mechanism of mesoderm spreading in *Drosophila* embryos. *Development* **132:** 491–501.

Winberg ML, Tamagnone L, Bai J, Comoglio PM, Montell D, Goodman CS. 2001. The transmembrane protein Off-track associates with Plexins and functions downstream of Semaphorin signaling during axon guidance. *Neuron* **32:** 53–62.

Wolf C, Schuh R. 2000. Single mesodermal cells guide outgrowth of ectodermal tubular structures in *Drosophila*. *Genes Dev* **14:** 2140–2145.

Wolf C, Gerlach N, Schuh R. 2002. *Drosophila* tracheal system formation involves FGF-dependent cell extensions contacting bridge-cells. *EMBO Rep* **3:** 563–568.

Wolff T, Ready DF. 1993. Pattern formation in the *Drosophila* retina. In *The development of Drosophila melanogaster*, pp. 1277–1325. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

Wouda RR, Bansraj MRKS, de Jong AWM, Noordermeer JN, Fradkin LG. 2008. Src family kinases are required for WNT5 signaling through the Derailed/RYK receptor in the *Drosophila* embryonic central nervous system. *Development* **135:** 2277–2287.

Wu M, Sato TN. 2008. On the mechanics of cardiac function of *Drosophila* embryo. *PLoS ONE* **3:** e4045.

Xu C, Kauffmann RC, Zhang J, Kladny S, Carthew RW. 2000. Overlapping activators and repressors delimit transcriptional response to receptor tyrosine kinase signals in the *Drosophila* eye. *Cell* **103:** 87–97.

Yao Y, Wu Y, Yin C, Ozawa R, Aigaki T, Wouda RR, Noordermeer JN, Fradkin LG, Hing H. 2007. Antagonistic roles of Wnt5 and the Drl receptor in patterning the *Drosophila* antennal lobe. *Nat Neurosci* **10:** 1423–1432.

Yoshikawa S, Bonkowsky JL, Kokel M, Shyn S, Thomas JB. 2001. The derailed guidance receptor does not require kinase activity in vivo. *J Neurosci* **21:** RC119.

Yoshikawa S, McKinnon RD, Kokel M, Thomas JB. 2003. Wnt-mediated axon guidance via the *Drosophila* derailed receptor. *Nature* **422:** 583–588.

Yu JY, Reynolds SH, Hatfield SD, Shcherbata HR, Fischer KA, Ward EJ, Long D, Ding Y, Ruohola-Baker H. 2009. Dicer-1-dependent Dacapo suppression acts downstream of insulin receptor in regulating cell division of *Drosophila* germline stem cells. *Development* **136:** 1497–1507.

Zeitouni B, Sénatore S, Séverac D, Aknin C, Sémériva M, Perrin L. 2007. Signalling pathways involved in adult heart formation revealed by gene expression profiling in *Drosophila*. *PLoS Genet* **3:** e174.

Zettervall C-J, Anderl I, Williams MJ, Palmer R, Kurucz E, Ando I, Hultmark D. 2004. A directed screen for genes involved in *Drosophila* blood cell activation. *Proc Natl Acad Sci* **101:** 14192–14197.

Zhang J, Lefebvre JL, Zhao S, Granato M. 2004. Zebrafish unplugged reveals a role for muscle-specific kinase homologs in axonal pathway choice. *Nat Neurosci* **7:** 1303–1309.

Zhang B, Luo S, Wang Q, Suzuki T, Xiong WC, Mei L. 2008. LRP4 serves as a coreceptor of agrin. *Neuron* **60:** 285–297.

Zhang L, Luo J, Wan P, Wu J, Laski F, Chen J. 2011. Regulation of cofilin phosphorylation and asymmetry in collective cell migration during morphogenesis. *Development* **138:** 455–464.

Zito K, Parnas D, Fetter RD, Isacoff EY, Goodman CS. 1999. Watching a synapse grow: Noninvasive confocal imaging of synaptic growth in *Drosophila*. *Neuron* **22:** 719–729.