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Drosophila as a Model for Context-Dependent Tumorigenesis

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Drosophila can exhibit classic hallmarks of cancer, such as evasion of apoptosis, sustained proliferation, metastasis, prolonged survival, genome instability, and metabolic reprogramming, when cancer-related genes are perturbed. In the last two decades, studies in flies have identified several tumor suppressor and oncogenes. However, the greatest strength of the fly lies in its ability to model cancer hallmarks in a variety of tissue types, which enables the study of context-dependent tumorigenesis. We review the organs and tissues that have been used to model tumor formation, and propose new strategies to maximize the potential of *Drosophila* in cancer research.

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Somatic mutations occur sporadically during ones lifetime (Greenman et al., 2007). If these somatic mutations disrupt the function of an oncogene or tumor suppressor gene they can result in cancer phenotypes. Organisms with short lifespans, such as the fruit fly, *Drosophila melanogaster*, do not normally develop cancer. The number of cell divisions that occur in their lifetime is much lower than a human who needs to maintain their tissues over long-periods of time. This fact may preclude them from naturally acquiring mutations leading to cancer. However, *Drosophila* can exhibit classic hallmarks of cancer, such as evasion of apoptosis, sustained proliferation, metastasis, prolonged survival, genome instability, and metabolic reprogramming (Hanahan and Weinberg, 2000, 2011; Luo et al., 2009) when cancer-related genes are perturbed.

Drosophila has been an instrumental model organism in the identification of cancer-related genes. Fruit flies have also uncovered many of the molecular mechanisms utilized by cancer-related proteins through the ingenuity of genetic tools that allow careful dissection of signaling pathway interactions. Using these tools the fly is capable of modeling many hallmarks of cancer in various tissues. The combination of the UAS/Gal4 binary expression system (Brand and Perrimon, 1993), the FLP-FRT recombinase system (Golic and Lindquist, 1989; Xu and Rubin, 1993), and the availability of RNAi transgenic animals make *Drosophila*, arguably, a powerful organism for investigating tumorigenesis. Not only can various tissues demonstrate classic hallmarks of cancer (Hanahan and Weinberg, 2000, 2011; Luo et al., 2009), but some of the most highly implicated pathways in human tumorigenesis, including Notch (N), Hedgehog (Hh), and Salvador/Warts/Hippo (SWH) were first identified in the fly (reviewed in Perrimon et al., 2012). In addition, the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway was observed to cause overgrowth in fly hemocytes prior to the discovery of its role in human leukemia (Harrison et al., 1995). *Drosophila*'s success at elucidating genes involved in tumorigenesis continues to provide promising targets for treatment of many human cancers. However, their greatest potential lies in their ability to model context dependency.

Cancer can develop in any tissue of the body with each tissue providing a different environment for tumor formation. Therefore, it is not surprising that tumor suppressors and oncogenes that cause cancer in one tissue type may produce no phenotype in another. One study demonstrated this by using cancer network reconstruction algorithms to predict driver mutations reported in breast cancer, colorectal cancer, and glioblastomas (Torkamani and Schork, 2009). In each tissue a distinct group of driver mutations were identified, in either Wnt/TGF-beta cross talk, the Wnt/VEGF signaling, or the MAPK/focal adhesion kinase pathways, respectively (Torkamani and Schork, 2009). Given that *Drosophila* can model many hallmarks of cancer in a variety of tissues, this organism is an ideal model to study the context dependency of tumor suppressors and oncogenes (Table 1).

In this review, we will highlight organ systems in *Drosophila* that have become desirable models for the study of established cancer hallmarks. We will then conclude by proposing a new oncogenic screening strategy with potential for additional identification of tumor suppressors and oncogenes in a tissue-specific context.

Adult Wing and Wing Imaginal Disc

The wing imaginal disc has and continues to be a superior model system for the identification and study of invasive growth. There are a variety of wing specific drivers that promote expression in particular segments or boundaries of the wing. These tools allow genes to be overexpressed, or knocked down in a defined group of cells followed by subsequent investigation of the neighboring wild type cells. For example, Vidal et al. (2006) took advantage of this system to examine the ability of cells lacking C-terminal SRC kinase (Csk) to invade surrounding wild type tissue. Similar studies using this metastatic model revealed that Jun N-terminal kinase (dJNK)

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TABLE 1. *Drosophila* context-dependent cancer-related tumor suppressor and oncogenes discussed in this review

Drosophila tissue/organ			*Drosophila* Cancer-Related Genes		
			Oncogenes	Tumor Suppressors	Examples of Synergy
	Wing/wing disc		Abl, dJNK, Mef2, N, $dRas^{V12}$, Sik2, Sik3, Src, yki	Csk, ft, hpo, hyd, sav, wts	Csk, Abl Csk, dJNK N, Mef2 Src, $dRas^{V12}$
	Eye/eye disc		crb, Mef2, dJNK, N, $dRas^{V12}$	ex, dlg, l(2)gl, Mer, mop, sav, scrib, wts	dJNK, scrib N, Mef2 scrib, $dRas^{V12}$
	Ovaries			dlg, l(2)gl, Ikb1, scrib	dlg, l(2)gl, scrib
	Brain	Neurons		aur, brat, dlg, l(2)gl, l(3)mbt, mira, Pins, polo, pros, scrib	
		Glia	Egfr, Fgfr, dMyc, PI3K	Rbf	Egfr, dMyc Egfr, PI3K Egfr, Rbf
	Hemocytes		Hh, JAK (hop)/STAT, dJNK pathways, Wg		
	Muscle		PAX7/FKHR, $dRas^{V12}$		PAX7/FKHR, $dRas^{V12}$
	Midgut		Egfr, Hpo (yki), dJNK, JAK/STAT, N, Wg pathways		JAK/STAT, Egfr JAK/STAT, Hpo (yki)

activation enhances the proliferative phenotype of these cells, whereas dJNK inactivation via Puckered overexpression inhibits apoptosis in these invasive cells (Vidal et al., 2006). These studies were continued and later suggested a dose dependent role of Src in Ras^{V12} induced tumor proliferation and metastasis (Vidal et al., 2007). Using the same system, a similar synergistic interaction between the *Csk* and *Abelson* (*Abl*) genes was demonstrated in the wing disc (Singh et al., 2010).

Many components of the major SWH growth-controlling pathway have been studied in the imaginal wing discs. Hyperplastic growth has been observed in mutant *warts*/*lats* (*wts*) (Justice et al., 1995), *fat* (*ft*) (Mahoney et al., 1991), *hyperplastic discs* (*hyd*) (Mansfield et al., 1994), and *hippo* (*hpo*) (Wehr et al., 2012) cells. These phenotypes are similar to those observed in the eye imaginal disc by manipulation of fellow pathway members. The wing disc has also been useful in identifying new modulators of the SWH pathway. Recently, Salt-inducible kinases (Sik2 and Sik3) were characterized as negative regulators of Hippo signaling in *Drosophila*. Activation of Sik kinases resulted in tissue overgrowth via regulation of SWH components Yorkie (Yki) and Salvador (Sav) (Wehr et al., 2012).

Undeniably, one of the most studied genes in the *Drosophila* wing is *Notch* (*N*). The "notched" wing phenotype associated with the loss of this gene was first observed in the early 1900s (Morgan, 1917). Although the alleles of *Notch* were identified in 1917 (Morgan, 1917), cloning and in depth analysis did not begin until the 1980s (Wharton et al., 1985; Kidd et al., 1986). Since this time, Notch pathway components and interactors have been identified through molecular and genetic studies (reviewed in Artavanis-Tsakonas et al., 1995; Bray, 2006; Hurlbut et al., 2007; Borggrefe and Oswald, 2009; Fortini, 2009; Artavanis-Tsakonas and Muskavitch, 2010; Andersson et al., 2011), much of which have utilized the wing as a model system. It has been established that Notch activity controls cell fate throughout development (reviewed in Artavanis-Tsakonas et al., 1995). However, it was first shown in the wing imaginal disc to not only regulate cell differentiation, but also affect cell proliferation (Go et al., 1998; Baonza and Garcia-Bellido, 2000). It has additionally been suggested to promote proliferation and metastasis in the wing disc through synergism with *Myocyte enhancer factor 2* (*Mef2*), in the same fashion as observed in the eye imaginal disc (Pallavi et al., 2012). This recent finding adds to the list of similar synergistic relationships promoting proliferation reported in the adult eye and eye imaginal disc (Moberg et al., 2005; Ferres-Marco et al., 2006), and wing imaginal disc (Vallejo et al., 2011).

Adult Eye and Eye Imaginal Disc

The *Drosophila* eye has been a classical tissue for studying gene function and performing genetic screens. Mutations in the adult eye and larval eye imaginal discs can result in a variety of visible, and easy to score, phenotypes without causing lethality. Numerous screens have used the eye to identify genes involved

in growth, proliferation, and/or metastasis (Rorth, 1996; Tseng and Hariharan, 2002; Bach et al., 2003; Pagliarini and Xu, 2003; Menut et al., 2007; Pallavi et al., 2012). In particular, studies in imaginal discs by Pagliarini and Xu (2003) investigated potential genetic interaction between the tumor suppressor *scribble* (*scrib*) and the oncogene d*Ras*. This study determined that overexpression of dRas^{V12} or loss of Scrib activity alone could cause increased growth in the eye but not result in metastasis. However, crosses of flies overexpressing dRas^{V12} with flies mutant for *scrib* (*Ras*^{V12}; *scrib*$^{-/-}$) generated animals with both an increase in growth, and acquired metastatic properties (Pagliarini and Xu, 2003). Brumby and Richardson also demonstrated similar interactions and further elucidated, by the use of genetic clones, dJNK regulation in the control of proliferation of *scrib* mutant tissue (Brumby and Richardson, 2003). More recently *scrib* mutant imaginal disc clones have been shown to promote growth and invasion when adjacent to d*Ras*^{V12} mutant clones, demonstrating oncogenic cooperation between different mutant cell populations (Wu, 2010). Collectively, these studies in the *Drosophila* adult eye and eye imaginal disc have identified cancer-related genes and demonstrated cooperative tumorigenesis between tumor suppressors and oncogenes. These studies of neoplastic proliferation in the eye imaginal disc revealed *Drosophila* as a tractable model of four "hallmarks of cancer" (Hanahan 2000, 2011), (1) sustained cell proliferation, (2) evasion of apoptosis, (3) loss of differentiation, and (4) metastasis or tissue invasion (Gateff, 1978; Woodhouse et al., 1998; Bilder et al., 2000; Brumby and Richardson, 2003; Pagliarini and Xu, 2003; Grzeschik et al., 2007; Zhao et al., 2008; Wu et al., 2010). Since the study of the "Scribble polarity module," composed of tumor suppressor genes *scrib*, *lethal (2) giant larvae* (*l(2)gl*), and *discs large* (*dlg*), additional proteins involved in apical–basal cell polarity, such as the "Crumbs (Crb) complex" have also been implicated in proliferation phenotypes in imaginal discs (Lu and Bilder, 2005), and suppression of apoptosis in the eye imaginal disc (Grzeschik et al., 2007).

Tumor suppressors that do not disrupt apical–basal polarity but still cause hyperplastic overgrowth in the adult eye and/or eye imaginal disc have also been identified. Some of these are members of the SWH tumor suppressor pathway, including *wts* (Xu et al., 1995), *shar-pei* (*sav*) (Kango-Singh et al., 2002), and *myopic* (mop) (Gilbert et al., 2011). Additionally, mutations in proteins acting upstream of Hpo and Wts, Merlin (Mer), and Expanded (Ex), have been shown to increase cell proliferation by either inhibiting apoptosis or delaying cell cycle exit, respectively (Pellock et al., 2007). Thus, *Drosophila* has been an excellent model for illustrating how mutations in SWH pathway genes do not disrupt cell architecture but are able to increase survival and proliferation.

Interestingly, Notch has also been shown to strikingly affect proliferation, differentiation, and apoptosis in many tissues throughout development (Artavanis-Tsakonas et al., 1995; Bray, 2006; Kopan and Ilagan, 2009; Artavanis-Tsakonas and Muskavitch, 2010). A recent screen in the adult eye identified a novel synergistic interaction between *Notch* and *Mef2* that further promotes proliferation and metastasis via inappropriate activation of the dJNK signaling pathway (Pallavi et al., 2012).

The *Drosophila* eye remains one of the best systems to study oncogenic gene interactions. Manipulation of cells within the eye has little to no affect on the viability of the organism. One can also study tumor microenvironments through the generation of clones. Clonal analysis allows direct comparison between genotypically diverse cells within the same animal and same tissue. These properties of the eye allow the study of otherwise lethal cancer-related genes, as well as allow the dissection of non-cell autonomous versus cell autonomous gene functions.

Adult Female Ovaries

One of the characteristics of epithelial-derived cancers is the loss of cell polarity and tissue organization. Some of the first well-described apical–basal polarity genes that regulate epithelial tissue organization were studied in the *Drosophila* ovaries, and developing embryos (Jacob et al., 1987; Woods and Bryant, 1991; Strand et al., 1995; Goode and Perrimon, 1997; Bilder and Perrimon, 2000; Bilder et al., 2000). The "Scribble polarity module" was shown to work together to properly control cell polarity and cell growth (Bilder et al., 2000). More importantly this study was one of the first to demonstrate cooperative tumorigenesis between multiple tumor suppressors. The follicle cells of the adult female ovary have also been used as a model organ to study other polarity related genes.

lkb1, homolog of human tumor suppressor gene *LKB1*, was identified in a germ line clone screen as a regulatory protein involved in anterior–posterior axis formation and epithelial polarity of the oocyte (Martin and St Johnston, 2003). Follicle cells in the adult female ovary mutant for *lkb1* were defective in polarity, and the normal follicular monolayer appeared to be rounded up (Martin and St Johnston, 2003). This work suggested that loss of polarity may in part account for tumorigenesis associated with human cancers caused by mutations in LKB1, such as Peutz–Jeghers syndrome (Martin and St Johnston, 2003).

Drosophila ovarian follicle stem cells (FSCs) have more recently been used to study adult stem cell behavior (Wang et al., 2012). Understanding FSC regulation has become increasingly important as adult stem cells have been implicated in cancer induction, resistance to chemotherapeutic treatments, and cancer recurrence (Reya et al., 2001; Dean, 2006; Kangsamaksin et al., 2007; Bonnet, 2008; Eyler et al., 2008; Fillmore and Kuperwasser, 2008; Todaro et al., 2008; Diehn and Majeti, 2010; Forsberg et al., 2010; Moore, 2010; Karamboulas and Ailles, 2012). *Drosophila* ovaries are an excellent system for studying stem cell biology due to the presence of both FSCs and germline stem cells (GSCs) located within stable niches at the tip of the ovarioles (Morrison and Spradling, 2008). In the era of RNAi, and the availability of fly lines allowing tissue-specific gene expression, screens for genes involved in both FSC and GSC maintenance and regulation are feasible. These types of studies will provide insight into cancer stem cell properties.

Larval Brain

The *Drosophila* brain has been used to study the regulation of neural stem cells, as well as model a malignant form of brain cancer, glioblastoma multiforme (GBM). Mutations in a number of genes, such as *lethal (3) malignant brain tumor* (*l(3)mbt*), *brain tumor* (*brat*), *dlg*, *l(2)gl*, *scrib*, *prospero* (*pros*), *miranda* (*mira*), and *partner of inscuteable* (*pins*), involved in the regulation of proliferation and development in the larval fly brain lead to malignant neoplastic tumors (reviewed in Froldi et al., 2008; Januschke and Gonzalez, 2008; Miles et al., 2011). These genes have been identified through genetic manipulation of the larval brain. Within the developing brain neuroblasts act as neural stem cells to derive all glia cells and neurons. Fly neuroblasts are one of the most well-characterized models of adult stem cells (Doe, 2008; Neumuller and Knoblich, 2009).

Neuroblasts

Renewal of stem cells and stem cell differentiation is kept in balance in part by asymmetric cell division (reviewed in Morrison and Kimble, 2006). This balance is crucial to prevent over proliferation, which may lead to cancer (Caussinus and

Gonzalez, 2005; Bello et al., 2006; Betschinger et al., 2006; Lee et al., 2006a,b). Genes such as *brat* (Bello et al., 2006) and *pros* (Choksi et al., 2006) have been identified as regulators in the balance between self-renewal and differentiation in the fly neuroblast. In addition to these genes, the tumor suppressor, Numb, was found to be distributed asymmetrically in the differentiating daughter cell during *Drosophila* neuroblast divisions (Rhyu et al., 1994; Knoblich et al., 1995). Further investigation of neuroblast regulation identified Polo kinase (polo), and Aurora kinase (aur) as tumor suppressors in the larval brain that participate in proper localization of Numb in differentiating daughter cells (Lee et al., 2006a; Wang et al., 2006, 2007). These centrosome-regulatory proteins ensure the proper distribution of Numb, which is required for the appropriate inhibition of Notch in the neuroblast daughter cell that continues on to differentiation (Wang et al., 2007). Daughter cells lacking Numb express Notch, and thus continue proliferating (Wang et al., 2007). It appears that centrosome function also plays a role in the regulation of asymmetric division of the neuroblast. It has been demonstrated that centrosome amplification (Basto et al., 2008) and centrosome dysfunction (Castellanos et al., 2008) can lead to neural stem cell tumors resulting from non-asymmetrical division, most likely via an increase in self-renewing daughter cells at the expense of differentiating daughter cells.

In a recent genome-wide transgenic RNAi screen, 620 genes were identified in the regulation of neural stem cells in *Drosophila* (Neumuller et al., 2011). This robust screening design revealed genes involved in splicing control, transcriptional elongation, and chromatin remodeling to be critical for neuroblast differentiation and self-renewal. The findings from this work add to our understanding of how stem cell homeostasis is achieved and elucidate potential targets for cancer stem cell treatments.

Glial cells

Tumors composed of glial cells, termed gliomas, are the most common type of human brain tumor, and unfortunately the most malignant (Louis et al., 2007). In an effort to better understand the biology of these rapidly proliferating, aggressively invasive, and highly treatment resistant tumors, *Drosophila* models have been established (Read et al., 2009; Witte et al., 2009). Since one of the most commonly mutated genes in gliomas is the *epidermal growth factor receptor* (*Egfr*) (Maher et al., 2001; Furnari et al., 2007), gliomas were induced in fly larval brains by the overexpression of receptor tyrosine kinases (RTK), such as Egfr, or fibroblast growth factor receptor (Fgfr), as well as other RTK activated proteins such as phosphatidylinositol 3-phophate kinase (PI3K) (Witte et al., 2009), via the UAS/Gal4 system. In each case enhanced proliferation of glial cells and/or metastasis of glial cells to eye imaginal disc, the optic nerve, and the optic stock were observed (Witte et al., 2009). Coactivation of Egfr and PI3K in *Drosophila* glia also was shown to cause neoplastic growth and invasion in a separate study (Read et al., 2009). In these experiments the glioma phenotype could also be observed by replacing overexpression of PI3K with either Diminutive (dMyc) overexpression or retinoblastoma (Rbf) loss of function (Read et al., 2009). The successful recapitulation of the human glioma phenotype through genetic manipulation of previously implicated genes suggests the fly glia as a promising model for the study of these tumors and the identification of specific targets for drug treatments.

Hematopoietic System

Hematopoietic stem cells (HSCs) are tightly controlled by their microenvironment to promote either self-renewal or differentiation into the various blood and immune cell lineages (Schofield, 1978; Dykstra et al., 2007). Disruption in this regulation results in human cancers, such as acute myeloid leukemia (AML) (Bonnet and Dick, 1997; Reya et al., 2001). To investigate the genetic determinants of these diseases the HSC niche is being rigorously studied. Flies have a distinct advantage over mammalian systems as a model to explore HSCs due to their lack of bone marrow. The complexity of the bone marrow itself, which houses HSCs in humans and other vertebrates, has delayed our ability to fully understand how HSCs are regulated. In flies stem-like hemocyte precursors or prohemocytes are located in a specific area of the lymph gland called the posterior signaling center (PSC) (Lebestky et al., 2003; Jung et al., 2005), and provide a much simpler system to study how cell autonomous and cell non-autonomous signals dictate HSC fate.

From *Drosophila* studies we know that a number of pathways act to control prohemocyte proliferation and differentiation. A *Drosophila* gain of function mutant of a JAK gene, *hopscotch* (*hop*), was found to cause proliferation of blood cells and lead to the formation of melanotic tumors in the lymph gland (Hanratty and Dearolf, 1993; Harrison et al., 1995). This was the first study to demonstrate that JAK/STAT signaling could result in tumorigenesis, and preceded the finding that the human protein JAK is overexpressed in leukemia (Lacronique et al., 1997). Since this initial finding the Hh pathway, the Wingless pathway (Wg) and the JNK pathway have all been identified as regulators of prohemocyte fate (Mandal et al., 2007; Owusu-Ansah and Banerjee, 2009; Sinenko et al., 2009). Wg signaling was shown to promote proliferation of prohemocytes and prevent differentiation (Sinenko et al., 2009). This was concluded by studies demonstrating that inhibition of Wg signaling resulted in fewer PSC cells than observed in control flies, and accordingly, increased activation of Wg signaling produced more PSC cells (Sinenko et al., 2009). The Hh pathway was shown to play a similar role (Mandal et al., 2007). Loss of Hh signaling leads to complete differentiation of hemocyte precursors and thus loss of stem-like hemocytes (Mandal et al., 2007). The pathways discussed thus far function to prevent differentiation. Work by a separate group investigated pro-differentiation signals (Owusu-Ansah and Banerjee, 2009), and found that reactive oxygen species (ROS) plays a role in triggering prohemocyte differentiation, and mediates this effect through the JNK signal transduction pathway. dJNK was shown to function downstream of ROS in the initiation of this process by dominant negative studies, which indicated that loss of dJNK function in the presence of ROS prevented differentiation of prohemocytes. Collectively, these studies established *Drosophila* PSC as a less complex niche and suitable model for the study of HSCs.

Larval Muscle

Although not a common tissue for the study of tumorigenesis, the muscle of the *Drosophila* larval gut has been used to model alveolar rhabdomyosarcoma (ARMS), an aggressive myogenic-type tumor resulting from misexpression of PAX3/7-FKHR fusion oncoproteins (Barr, 2001; Galindo et al., 2006). The beauty of the *Drosophila* larval muscle system lies in its transparency. Fluorescent protein reporters can be visualized through the larval outer cuticle in real-time and without need for dissection. Galindo, Allport, and Olson took advantage of this attribute to study PAX7 (gsb)/FKHR function in the muscle (Galindo et al., 2006). They were able to investigate PAX7/FKHR activity in vivo for the first time, and demonstrate its ability to interrupt differentiation of muscular tissue resulting in

new cells being formed from myofibers (Galindo et al., 2006). These new cells are then able to invade surrounding tissue and migrate to other body organs, such as the central nervous system (Galindo et al., 2006). Further analysis of these cells revealed that the constitutively active oncogene, $dRas^{V12}$, could enhance this phenotype. This is most likely due to the ability of both dRas and PAX7/FKHRs to disrupt muscle differentiation (Galindo et al., 2006). This work establishes the *Drosophila* larval muscle as a unique system to study ARMS, and could be a powerful tool for the identification of additional genes involved in the mechanics of this disease.

Adult Midgut

Interest in epithelial stem cell (SC) maintenance, proliferation, and differentiation has exploded since regulation and function of these stem cells has been implicated in tumor malignancy and cancer stem cells (Reya et al., 2001; Dean, 2006; Kangsamaksin et al., 2007; Bonnet, 2008; Eyler et al., 2008; Fillmore and Kuperwasser, 2008; Todaro et al., 2008; Diehn and Majeti, 2010; Forsberg et al., 2010; Moore, 2010; Karamboulas and Ailles, 2012). *Drosophila* intestinal SCs (ISCs) are an attractive system for the study of adult somatic stem cells in vivo. Roughly 1,000 ISCs are housed among the 10,000 cells in the posterior midgut epithelium, and can be identified by the expression of Notch ligand Delta (Dl) (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). ISCs divide to generate enteroblasts (EBs) that differentiate into either enteroendocrine cells (EEs) marked by Pros expression, or enterocytes (ECs) marked by Pdm1 (Nub) expression (reviewed in Sahai-Hernandez, 2012). Study of these cells is done primarily through lineage tracing (Morrison and Spradling, 2008), which is easily achieved in the fly by utilizing the UAS/Gal4/Gal80 expression system (Lee and Luo, 1999; Suster et al., 2004) to follow cells over time. Since first identified in 2006, numerous signaling pathways have been found to regulate ISC proliferation and differentiation in the fly.

As described previously, Notch signaling plays an important role in regulating cell differentiation. In the ISCs Notch is expressed in both daughter cells, but the nonstem daughter cell expresses lower levels of the Notch ligand, Dl. This results in the acquired EB fate of the nonstem cell, which displays increased Notch activity (Bardin et al., 2010). Data also suggests that the level of Dl determines whether the EB cell will differentiate into EE or EC cells (Ohlstein and Spradling, 2007). Although many questions still remain, it is clear that differential activation of Notch signaling is essential to maintain the proper balance between differentiation and self-renewal.

While Notch regulates cell differentiation, many other pathways cooperate with partial redundancy to promote ISC proliferation and maintenance. Wg signaling is required in the ISCs to maintain the SC niche and promote proliferation (Lin et al., 2008). This was validated by the loss of negative regulators of the Wg pathway resulting in tumor formation, and the loss of positive regulators demonstrating reduced division of ISCs (Lin et al., 2008; Lee et al., 2009). The role of Wg in ISC regulation appears to be restricted to promoting self-renewal, as EB differentiation into EE or EC cells is not affected by loss of pathway activity (Xu et al., 2011). Egf signaling plays a similar role in the ISC niche. It has been shown in the fly that reductions in Egfr pathway activity reduces ISC proliferation (Jiang et al., 2011; Xu et al., 2011), but shows little to no affect in differentiation (Xu et al., 2011).

ISC proliferation is additionally regulated by feedback from ECs, which are sensors of damage and injury (Jiang et al., 2009; Staley and Irvine, 2010). Fly studies have revealed that dJNK activates JAK/STAT signaling in ISCs by the release of Unpaired (Upd) cytokines from dying ECs (Jiang et al., 2009). JAK/STAT activation increases the proliferation of ISCs to replace and maintain the EC population. The Hpo pathway is also activated in response to stress induced signaling by dJNK in ECs (Staley and Irvine, 2010). However, the role of Hpo in the SC niche is more complex due to its activity in not only ECs but also ISCs (Karpowicz et al., 2010; Staley and Irvine, 2010). A study in 2010 revealed that Yki activation is critical for proliferation of ISCs after gut damage (Karpowicz et al., 2010). While Hpo components Fat and Dachsous (Ds) normally inhibit Yki to limit ISC proliferation, in the case of damage Yki is activated by Hpo pathway inhibition (Karpowicz et al., 2010). Regulation of the aforementioned pathways is essential for the maintenance of SC populations and prevention of tumor formation.

Concluding Remarks

In this review we have selected examples from *Drosophila* demonstrating the insights that can be gained from studying oncogenes and tumor suppressor genes in various tissues and organs. The diverse roles of these cancer-related genes emphasize the importance of context, with each tissue providing a different environment for tumor formation. Importantly, screens for cancer-related genes in the fly have yet to be fully realized. Indeed, screens for oncogenes have not yet been systematically performed because mutations in these genes are associated with dominant lethality, and screens for tumor suppressors have not been done in different cell types.

Recently, transposon and retrovirus-based insertional mutagenesis screens have been used in the mouse to identify new candidate tumor suppressors and oncogenes present in somatic tumors (reviewed in Copeland and Jenkins, 2010). This approach is especially important today as it is now clear that the spectrum of mutated genes in a tumor is complex and varies from tissues to tissues. Despite its promises, the limitation of the genetic tools available in the mouse together with the expense associated with mammalian experiments present significant obstacles to the large-scale application of this approach. Adapting this screening strategy for use in the fly could lead to the identification of new tumor suppressors and oncogenes. Mobilization of *piggyBac* elements carrying upstream activation sequences (UAS) in specific tissues can be accomplished by expressing *piggyBac* transposase under heat-shock control. This "jumping" of transposons will result in either gene inactivation or ectopic expression in specific tissues via the UAS/Gal4 system (Brand and Perrimon, 1993). The fly holds an additional advantage over mammalian models due to the established FLP-FRT system (Golic and Lindquist, 1989; Xu and Rubin, 1993) for the generation of homozygous clones. This genetic tool can be utilized to identify tumor suppressor genes that only show a phenotype when both copies of the gene are lost. Tumors formed in the tissue of interest could then be analyzed using Next Generation Sequencing to identify the genes affected by the induced mutagenic event. This type of screening strategy will not only identify new tumor suppressors and oncogenes but also provide important information on the contextual differences between tumor phenotypes in distinct tissues. This strategy could be further extended to screens in sensitized genetic backgrounds to identify genes functioning cooperatively or antagonistically in a particular signaling pathway. Altogether, the integration of newly emerged molecular technologies with *Drosophila*'s well-established genetic resources suggest an exciting future for the fly in cancer biology.

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