Regulation of proliferation, cell competition, and cellular growth by the *Drosophila* JAK-STAT pathway

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The JAK-STAT pathway is a key regulator of tissue size in *Drosophila melanogaster*. Here we provide an overview of its roles in processes that regulate the size of *Drosophila* imaginal discs, epithelia of diploid cells that proliferate and acquire specific fates in the larvae and that become functional in the adult. *Drosophila* has a single JAK and a single STAT gene, which has facilitated genetic dissection of this pathway. Moreover, the sophisticated genetic tools available in flies for clonal growth assays have made *Drosophila* an ideal organism in which to dissect the multiple roles of the JAK-STAT pathway in growth control. Studies in flies have revealed JAK-STAT pathway activity as a central node for diverse signals that control proliferation and mass accumulation. In addition, recent work has established a new role for the pathway in cell competition, a process thought to be akin to the early stages of transformation in which more robust cells kill and take the place of less robust ones.

**Background**

With only one JAK and one STAT, the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway has lower complexity in the fruit fly *Drosophila melanogaster* than in mammals.1 There are 3 interleukin-6 (IL-6)-like cytokines—Unpaired (Upd), also called Outstretched, Upd2, and Upd3. These ligands bind to the receptor Domeless (Dome), which is homologous to gp130, the common chain for the IL-6 receptor family (Fig. 1).2-5 There is a second transmembrane receptor, *eye transformer*, also called *latran*, which forms heterodimers with Dome and antagonizes JAK-STAT signaling.6,7 The sole *Drosophila* JAK, called Hopscotch (Hop), is most similar to JAK2, and the sole STAT, called STAT92E, is most homologous to STATs 3 and 5.8,10 Activated STAT92E dimers modulate expression of target genes, the best characterized of which is *Socs36E*, which encodes a negative regulator.11 The reduced genetic complexity of the pathway in *Drosophila* and the observation that numerous human disease genes are conserved in flies,12 make *Drosophila* an excellent model for studying this pathway.

It is well established that dominant-active mutations in JAK2 result in human leukemia and myeloproliferative disorders.13,14 In addition, sustained STAT3 signaling is linked to tumorigenesis in mouse models and a dozen types of human cancer, including all classes of carcinoma.15-17 Cytokine signaling is also important for normal organ size during development as mice deficient for *SOCS2*, a negative regulator of growth hormone signaling, exhibit gigantism.18 Roles of the JAK-STAT pathway in growth control have been well described in *Drosophila*. With the advantages of powerful genetic approaches and in vivo clonal growth assays, studies in *Drosophila* have advanced our knowledge of the importance of this pathway during development, homeostasis and transformation. In this review, we discuss the current understanding of the functions of the JAK-STAT pathway in the growth of imaginal discs.

**Growth Control during Development**

Imaginal discs are comprised of epithelial cells that give rise to the cuticular structures of the adult, such as compound eyes and wings. Each imaginal disc is formed from a small number of cells (e.g., 50 cells in the case of the wing disc) that are specified in the embryonic ectoderm.19 Once the embryo hatches into the larva, which promptly begins to feed, the discs start to grow rapidly. Larval development lasts ~4 d at 25 °C and consists of three distinct periods called instars, each separated by a molt. Imaginal disc cells proliferate exponentially during larval development to give rise to thousands of cells (e.g., 50,000 cells in the case of the wing disc) at the end of third instar.20,21 Most of the cells in the larva are polyploid, undergoing endoreplication (S phase but not cytokinesis) and increasing their volume substantially. In contrast, imaginal cells are diploid and undergo both S and M phase.

Growth in wild-type eye discs is mediated by an “organizer” which forms during second instar at the dorsal–ventral (D–V) midline through the actions of *Iroquois-Complex* (*Iro-C*) genes, which repress the O-glycosyltransferase Fringe (*Fng*) to the ventral domain (Fig. 2). This juxtaposition of ventral *fng* cells and dorsal *fng* cells leads to activation of Notch signaling.22-24 Notch signaling at the D–V midline is required for appropriate disc

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One important function of JAK-STAT signaling is in formation of the eye field; it promotes proliferation and growth of cells in the eye field while cell-autonomously repressing wingless (wg), which specifies head cuticle fate (see below).27,29,30,32,33 Interestingly, JAK-STAT signaling has been shown to act downstream of Notch signaling. Specifically, activated STAT92E represses expression of Serrate (Ser),34 which encodes a Notch ligand homologous to mammalian Jagged and which is normally restricted to the ventral eye (Fig. 2).22-24 The loss of Stat92E in clones in dorsal eye results in ectopic expression of Ser there and over-growth of this compartment.35 Finally, the expression of upd prior to the reported formation of the D–V organizer (described above) suggests that either the organizer is actually active in first instar or that upd can be induced independently of Notch signaling. In fact, one study did report an early role of upd in formation of the organizer, implying that JAK-STAT activity can also function upstream of Notch in the eye disc.35

Studies from several labs have since shown that STAT92E is a central regulator of eye size. The functional effects of sustained activation of the JAK-STAT pathway in imaginal discs was forecast fortuitously by transposon insertion in the Om(1E) gene, a paralog of upd, in the related species D. ananassae, resulting in increased Om(1E) expression and outgrowths in the adult eye.36 Subsequently, the role of sustained JAK-STAT pathway activation in tissue growth was confirmed by targeted mis-expression of upd in the developing eye disc of D. melanogaster; GMR-upd transgenic animals have enlarged eye imaginal discs, resulting in a dramatically enlarged compound adult eye.30 A characterization of GMR-upd and similar transgenic animals revealed that Upd acts as a mitogen for undifferentiated eye cells.30,32 The increased production of Upd ligand in GMR-upd animals expands the number of eye progenitor cells without affecting their patterning, leading to a distinctly larger eye that is otherwise patterned normally.30 The GMR-upd enlarged eye phenotype can be largely suppressed by halving the genetic dose of Stat92E, suggesting that activation of STAT92E downstream of Upd is primarily responsible for the overgrowth.30,32 Shortly after the publication of the GMR-upd animal, another study reported a similar enlarged-eye phenotype resulting from inactivation of C-terminal src kinase (Csk) function in the eye disc. STAT92E is autonomously activated in Csk−/− clones, suggesting that JAK-STAT signaling plays an important role in the Csk−/− over-grown eye.37 Indeed, this phenotype is largely suppressed by reducing Stat92E expression levels.37 The activation of STAT92E in Csk−/− clones is likely due to upregulation of Src kinases in the absence of negative regulation by Csk (as opposed to Csk-dependent activation of Dome or Hop), but this has not been formally shown. Of note, mutations in endosomal sorting complex required for transport (ESCRT) components tsg101 and vps25, which trap the Notch receptor in an activated state, also result in cell-autonomously increased in upd expression and dramatic eye over-growth, a phenotype that depends on STAT92E activation.38-40 In fact, a recent study of Notch-dependent hyperplastic wing imaginal disc tissue has revealed that all three upd ligands are direct targets of Notch signaling and their loci interact directly with the Notch transcriptional effector Suppressor of Hairless.41 As mentioned

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**Figure 1.** The Drosophila JAK-STAT pathway. Three Unpaired (Upd) ligands here collectively referred to as Upd (orange) activate a dimeric receptor Domeless (Dome) (magenta). This results in activation of the JAK Hopsens (Hop) (green), leading to tyrosine phosphorylation of Dome. The phosphorylated receptor/JAK complex phosphorylates STAT92E dimer (blue) on Y711, generating an active STAT92E dimer. A consensus TTCNNGAA site is bound by the activated STAT92E dimer, leading altered gene expression. One of the best-characterized STAT92E target genes is Socs36E, encoding a negative regulator of JAK/receptor activity (pink). A second receptor Eye Transformer (ET) (also called Latran (Lat)), referred to as ET/Lat (red), forms heterodimers with Dome and inhibits JAK-STAT signaling. Brown circles represent phosphoryl tyrosine residues.
above, although Notch is activated along the entire midline, upd is induced only at the posterior margin at the midline, i.e., only in a small region of active Notch signaling, indicating that other factors must repress its expression elsewhere in the disc. Interestingly, upd genes, particular upd3, are repressed by polycomb-group repressive complex 1 (PRC1) and are ectopically expressed in mutations in any PRC1 component, leading to eye-overgrowth that is suppressed by lowering the dose of Stat92E. 42, 43 Finally, in the Raf1/2/scribble (scrib) metastatic tumor model, Upd is upregulated by Jun N-terminal kinase (JNK) signaling, which leads to STAT92E activation in both the tumor and adjacent cells and is required for metastasis of the tumor from the eye disc to the ventral nerve cord. 44 Thus, restricting induction of Upd to the posterior midline by balancing Notch activation with PRC1 repression during development and JNK activation during tumorigenesis is important to prevent over-growth (Fig. 2).

**JAK-STAT Signaling and Proliferation**

Given the significant role of the JAK-STAT pathway in specification of eye size, a key issue is how this pathway controls proliferation. FACS analysis of cells from eye and wing discs with sustained JAK-STAT signaling revealed that these cells appear to progress through G1/S and G2/M cell cycle checkpoints faster than control disc cells. 29, 30 These results raise the possibility that JAK-STAT signaling controls the expression or activation of factors required for cell cycle progression. In fact, one study reported that cyclin-dependent kinase 4 (Cdk4) functions between Hop and STAT92E in the embryo. 45 However, in Drosophila Cdk4 is primarily a regulator of cellular growth (see below) and is dispensable for proliferation. 46-48 Cyclin B (CycB), which is required for G2/M progression in the embryo, 48 was elevated in a cell-autonomous manner in clones with increased JAK-STAT signaling. It is not known if CycB is a target of JAK-STAT signaling or if increased CycB in JAK-STAT pathway gain-of-function clones simply reflects increased proliferation rates. 33 In fact, two independent genetic screens failed to reveal a cell cycle gene that strongly modified the GMR-upd phenotype. 30, 33 While this could be due to the possibility that cell cycle genes are largely dosage-insensitive in the GMR-upd background, expression profiling of GMR-upd eye discs also did not reveal any potential candidates. 34 In addition, three independent whole-genome RNAi screens did not identify a connection between JAK-STAT signaling and genes known to regulate proliferation. 49-51

An anti-proliferative role has also been reported for STAT92E. One study reported that Stat92E−/− clones induced late in larval wing development grew to larger sizes than their sibling (+/+) clones. 39 The observation that hop−/− clones did not display the same overgrowth phenotype led to the model that in late larval wing discs, STAT92E acts non-canonically (i.e., independently of Upd or Hop) to constrain proliferation. 33 This study postulates that Drosophila STAT92E contains both the pro-proliferative function of STAT3 and the anti-proliferative function of STAT1 and that evolutionary forces subsequently assigned these roles to distinct mammalian STAT proteins. This paper raises important questions that need to be addressed. First, are there distinct regions of STAT92E that mediate these opposite effects on proliferation? Second, what factors are the pro-proliferative and anti-proliferative targets of STAT92E? Finally, the proposed switch from pro-proliferative to anti-proliferative occurs within a 24-h window. What changes occur in STAT92E or the chromatin of late larval wing imaginal disc cells to facilitate this switch? Our current understanding of JAK-STAT regulation of proliferation is limited, and more studies will be required at the molecular level to sufficiently answer these questions.

**JAK-STAT Signaling and Cell Competition**

Local interactions between cells influence their growth and their ability to contribute to the adult. Some of these interactions have been revealed by studying “cell competition”, a process that has been best studied in the Drosophila wing disc 52-54 but that also exists in mammals. 55, 56 In the last 10 years, the field of cell competition has exploded (reviewed in refs. 57 and 58), but a consensus on definitions for each type of competitive interaction has not yet been achieved. In this review, we will use the term “cell competition” to mean the context-specific behavior of cells of a
particular genotype: they are killed (out-competed) when surrounded by wild-type cells but viable when placed in the context of slower-growing cells. The first example of cell competition was observed with Minutes (M), dominant mutations in ribosomal protein (Rp) genes that are lethal when homozygous (M/M) but produce viable, slow-developing animals when heterozygous (M+/M) or M/+. M+/+ cells exhibit distinct outcomes depending on the local environment; M+/+ clones are viable when residing in a homotypic environment (i.e., when they are surrounded by M/+ cells) but die when grown in the presence of wild-type (+/+ cells). These studies also revealed that death of M+/+ cells is associated with proliferation of wild-type cells. The wild-type cells (termed “winners”) subsequently occupy the space of the M+/+ cells (termed “losers”), which are eliminated by the winners through cell death to ensure maintenance of normal tissue size. It has been subsequently shown that differences in levels of other growth-regulatory genes such as dMyc, a transcription factor that regulates expression of genes controlling proliferation, cellular growth, and ribosome biogenesis, elicit similar types of competitive interactions; clones with lower levels of dMyc become losers, which are killed by winners that have normal levels of dMyc.69,70

Knowing the dependence of proper cell growth and tissue development on STAT92E activity, clonal growth assays were employed to assess whether modulating the levels of JAK-STAT signaling could induce competitive interactions. Stat92E−/− clones and their wild-type (+/+ sibling clones were induced by FLP/FRT-mediated mitotic recombination62 early in embryonic development and clone size was measured in wing and eye discs after a defined period. Such disc cells are epithelial and remain associated after mitosis, differences in clone size reflect differential growth rates.63 If Stat92E were not required for clonal growth, Stat92E−/− clone areas should comprise ~50% of the total clone area. In one study, control FRT628 wild-type clones and their sibling clones grew to equal sizes and were each ~50% of the total clone area.29 By contrast, Stat92E−/− clones comprised only ~5% of the total clone area in the disc. In another study, Stat92E−/− clones induced during early larval development were larger [40% of the total clone area].31 The discrepancy in Stat92E−/− clone size is presumably due to the use of weaker Stat92E alleles in the latter study.31,33 By contrast, Stat92E−/− clones in a mosaic background underwent caspase-dependent but JNK-independent cell death and were extruded from the epithelium.29 However, when programmed cell death was blocked in the Stat92E−/− cells, they grew to the same size as sibling clones.29 By contrast, clones lacking dmyc or ribosomal genes like Rpl135 cannot grow even when death is inhibited.64,65 This may represent an important distinction between the function of activated STAT92E and dMyc in losers. The context-specific behavior of cells with reduced JAK-STAT signaling was revealed when Stat92E−/− clones were given a growth advantage. When induced in a Minute background, Stat92E−/− clones grew to large sizes.29 This result reveals that Stat92E−/− cells die in a wild-type background because they have become losers and are out-competed by the more robust wild-type winner cells. Similar results—that loss of Stat92E reduces cellular fitness and renders cells losers—have been observed in a scrib−/− tumor suppressor model in Drosophila.66

Cells with increased dMyc or increased Wingless (Wg) signaling become “supercompetitors”, which we define as a clone of cells overexpressing a particular factor that causes neighboring wild-type cells to experience a growth disadvantage.29,60,67,70 Of note, clones with increased dMyc expression kill losers up to 10 cells away.79 Clonal growth assays, such as the two-clone assay,79,81 which serve as a direct measurement of supercompetitor behavior, revealed that clones with sustained JAK-STAT pathway activation become winners, acquire supercompetitor characteristics, and can kill losers located several cell diameters away through non-autonomous induction of apoptosis.29 This study also demonstrated that, like with dMyc, cells with activated STAT92E activity require the pro-apoptotic gene head involution defective (hid) to kill surrounding neighbors and achieve supercompetitor status. These results suggest a link between STAT92E and dMyc or between STAT92E and the Wg pathway. Surprisingly, however, no link was found between JAK-STAT signaling and either dmyc mRNA, dMyc protein, or targets of the Hippo pathway,69 which regulate dMyc levels.68,69 In addition, clonal mis-expression of dMyc did not activate STAT, nor did clonal mis-expression of Crumbs,27,75 which is a target of JAK-STAT signaling in the embryo6 and an upstream regulator of Hippo pathway signaling. Finally, hyperactivation of JAK-STAT signaling had no effect on Wg signaling and, reciprocally, Wg did not modulate STAT92E activity.29 These results strongly suggest that at least in the wing imaginal disc JAK-STAT pathway activity functions in parallel to dMyc and Wg in growth and cell competition (Fig. 3).

**JAK-STAT Signaling and Cellular Growth**

Tissue growth occurs as a result of both cellular growth (also called mass accumulation) and subsequent proliferation. Studies from *Drosophila* imaginal discs have shown that cell division and cellular growth are regulated independently.65,75 It follows that in order to get overgrown imaginal tissue, both proliferation and cellular growth must be accelerated concomitantly. Numerous factors affect cell size, including dMyc, CycD/Cdk4, and Hippo.76 Since JAK-STAT signaling in the eye imaginal disc is causal for tissue overgrowth, it is of great interest to unravel how this pathway regulates cellular growth. We define cellular growth as the net production of new proteins, which can occur by a variety of means, including but not limited to increased de novo synthesis of ribosomes (i.e., ribosome biogenesis) or accelerated translation on existing ribosomes. Increased cell size can result from increased cellular growth and can be measured by the forward scatter parameter on a flow cytometer.64 FACS analysis of cells with sustained JAK-STAT signaling revealed no change in cell size.29,30 Consistent with this, there was no change in cell density in clones with activated JAK-STAT signaling.33 The unaltered cell size in cells with sustained JAK-STAT signaling is likely due to the fact that cell division rates are also increased when this pathway is hyper-activated.29,30,32,33 Furthermore, JAK-STAT signaling does not induce genes such as *nop5*, *nop60B*, and *Tif-1A* (which, incidentally, are targets of dMyc) that regulate de novo
ribosome biosynthesis.\textsuperscript{29} As mentioned above, the JAK-STAT pathway also does not interact with dMyc, which upregulates ribosome biogenesis,\textsuperscript{65} or regulators of dMyc.\textsuperscript{68,69} These data suggest that JAK-STAT signaling does not regulate cellular growth by means of increasing ribosome biogenesis. As mentioned above, one study reported that CycD/Cdk4 functions to promote proliferation and acts between Hop and STAT92E in JAK-STAT signaling. However, there are lines of evidence that suggest that this conclusion needs to be re-examined, particularly with respect to JAK-STAT signaling in imaginal discs. First, several groups have reported that CycD/Cdk4 is not required for proliferation but instead promotes growth through mitochondrial biogenesis.\textsuperscript{46,47,77} Second, we have not found a link between mitochondrial functions and JAK-STAT signaling (Rodrigues and Bach, unpublished data). Taken together, how JAK-STAT signaling controls cellular growth at the molecular level remains a critical area of investigation for the field.

Concluding Remarks

In summary, these studies have revealed that the JAK-STAT pathway is a central regulator of tissue size in Drosophila imaginal discs. In the eye disc, upd is subject to positive and negative regulation, but only Notch-mediated induction of upd has been delineated at the genetic level. Future work should reveal how JNK activates and how PRC1 represses the upd locus. Furthermore, the inhibitory effects of Csk on activated STAT92E also need to be further explored. Despite the central role that JAK-STAT signaling plays in proliferation and cellular growth, the targets of STAT92E required for these processes are yet unknown and need to be determined in future studies. Finally, the recent work showing that cells with sustained JAK-STAT activity become super-competitors raises several outstanding questions, including: (1) Do STAT92E winners secrete a Notum-like molecule, which inhibits neighboring cells from transducing Upd signals? (2) What are non-autonomous signals downstream of STAT92E that cause death in losers? (3) Are these signals regulated by other factors involved in cell competition such as dMyc and Wg signaling? Using Drosophila as a model to study how JAK-STAT signaling regulates proliferation, cellular growth, and cell competition is poised to shed light on mechanisms of tumorigenesis in mammals.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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