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# Functions of the Drosophila JAK-STAT pathway
## Lessons from stem cells

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JAK-STAT signaling has been proposed to act in numerous stem cells in a variety of organisms. Here we provide an overview of its roles in three well characterized stem cell populations in Drosophila, in the intestine, lymph gland and testis. In flies, there is a single JAK and a single STAT, which has made the genetic dissection of pathway function considerably easier and facilitated the analysis of communication between stem cells, their niches and offspring. Studies in flies have revealed roles for this pathway as diverse as regulating bona fide intrinsic self-renewal, integrating response to environmental cues that control quiescence and promoting mitogenic responses to stress.

### Background

The fruit fly *Drosophila melanogaster* has a single *jak* and a single *stat* gene, compared with four *JAK* and seven *STAT* genes in mammals.[1,2] The lack of genetic redundancy of the JAK-STAT pathway in flies, coupled with the fact that numerous human disease genes are conserved in flies,[3] make Drosophila an excellent model for studying this pathway. In Drosophila, three related interleukin-6 (IL-6)-like cytokines, Unpaired (Upd) also called Outstretched, Upd2 and Upd3, activate a gp130-like receptor Domeless (Dome) (**Fig. 1**). This leads to the activation of the JAK Hopscotch (Hop), which is most similar to JAK2, and the STAT STAT92E, most homologous to STATs 3 and 5. Activated STAT92E induces expression of target genes including *SOCS36E*, which encodes a negative regulator.[4] A second JAK-STAT receptor—*eye transformer* (*et*) also called *latran* (*lat*) and hereafter referred to as *et/lat*—has been identified.[5,6] Et/Lat forms heterodimers with Dome and antagonizes JAK-STAT signaling.

Sustained JAK activation is a causal event in human leukemia and myeloproliferative disorders (MPDs).[7,8] In addition, persistent activation of STAT3 is associated with tumorigenesis in mouse models and a dozen types of human cancer, including all classes of carcinoma.[9,10] The fact that significant therapeutic benefits are observed in some MPD patients treated with JAK2 inhibitors suggests that myeloid progenitor cells carrying the $JAK2^{V617F}$ activating mutation are the tumor propagating cell type in this disease.[11] Consistent with a role of the JAK-STAT pathway in hematopoiesis, mice and humans lacking *JAK3* or its critical receptor the γc chain present with severe combined immunodeficiency due to loss of lymphoid lineages.[12,13] Individual *JAK* and *STAT* knockouts have specific blocks in lymphoid or myeloid lineage commitment,[2] suggesting that—barring as yet untested genetic redundancies—this pathway does not play a critical role in hematopoietic stem cell (HSC) maintenance.

Leukemia inhibitory factor (LIF)/STAT3 signaling is able to maintain cultured murine embryonic stem cells (ESCs) that can contribute to chimeric animals.[14,15] Although LIF/STAT3 is not required for ESC pluripotency, LIF is routinely added to ESC cultures and is required for reprogramming epiblast stem cells derived from post-implantation embryos (EpiSCs) to an earlier pluripotency state (i.e., ESCs).[16,17] When considered together with the early embryonic lethality of *STAT3* knockout mice,[18] these results point to an important role of JAK-STAT signaling in maintenance of some stem cell populations during mammalian development.

Roles of the JAK-STAT pathway in stem/progenitor cell maintenance have also been described in Drosophila. With the advantages of well-defined stem cells and powerful genetic approaches, Drosophila has advanced our knowledge of the function of this pathway in stem cell self-renewal and differentiation. In this review, we discuss the current understanding of pathway activity in three of the best-studied stem cell systems in Drosophila: the intestine, the lymph gland (the fly hematopoietic organ) and the testis.

### Intestinal Stem Cells

The digestive systems of vertebrates and flies share numerous similarities.[19] In both cases absorptive cells [called enterocytes (ECs) in flies] comprise the majority of the intestinal epithelium. Interspersed are hormone-producing cells [called enteroendocrine (ee) cells in Drosophila] (**Fig. 2A**). In 2006, the existence of intestinal stem cells (ISCs) in the Drosophila adult midgut epithelium was reported.[20,21] Under homeostatic conditions, the Notch ligand Delta is highly expressed in ISCs and Notch signaling is prominent in enteroblasts (EBs), the ISC daughter cell that gives rise to EC and ee cells. Although there is no known transcriptional marker for ISCs, stem cell fate correlates with repression of canonical Notch targets like *E*(*Spl*).[22] Therefore, a Delta-Notch signal is essential for differentiation in the fly

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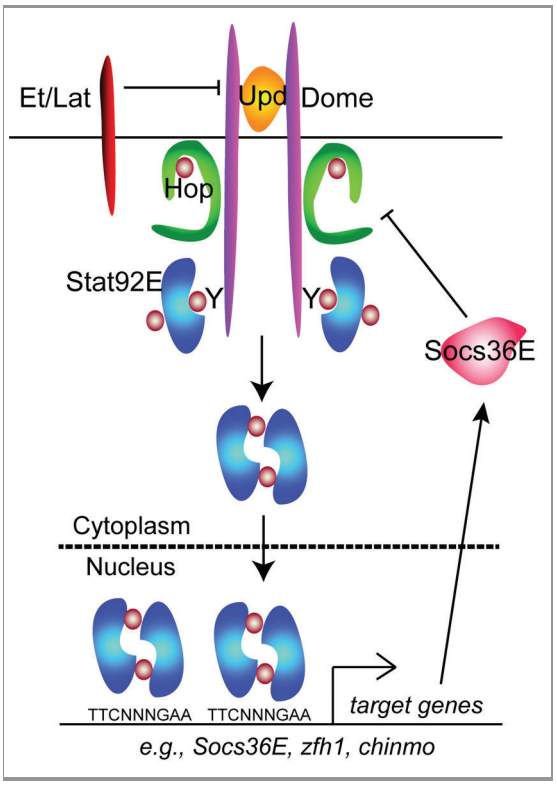


**Figure 1.** The Drosophila JAK-STAT pathway. The Drosophila JAK-STAT pathway consists of three Unpaired (Upd) ligands here collectively referred to as Upd (orange). The receptor Domeless (Dome) (magenta) is activated when Upd binds. This results in activation of the JAK Hopscotch (Hop) (green), leading to tyrosine phosphorylation (brown circles) of Dome. The phosphorylated receptor serves as a docking site for a STAT92E dimer (blue). Once bound, STAT92E is phosphorylated on tyrosine 711, generating an active STAT92E dimer that translocates to the nucleus, binds to a consensus TTCNNNGAA site, and alters gene expression. Some of the best-characterized STAT92E target genes are *SOCS36E*, *zfh1*, *chinmo*. *SOCS36E* (pink) encodes a negative regulator of Dome/JAK activity. 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.

midgut. Activity of the JAK-STAT pathway is highest in EBs.[23-25] These data suggest that under normal conditions, STAT92E function is required in EBs and their progeny—the EC and ee cells—and not in ISCs. Indeed, ISC clones that are mutant for *STAT92E* can divide to produce EBs but *STAT92E* deficient EBs cannot terminally differentiate.[23-26] These data show that both Notch and STAT92E are required for EB differentiation. Experiments to determine the epistasis between these pathways in EB differentiation have produced conflicting results. One group could not rescue differentiation within *STAT92E* mutant clones by mis-expressing an activated form of Notch,[23] while another group reported the opposite.[25] In fact, even the role of the JAK-STAT pathway in ISC self-renewal is controversial. Two groups reported that under homeostatic conditions JAK-STAT signaling is not required for ISC self-renewal,[23,24] but another group reports it is indeed essential for maintenance of these stem cells.[26] This latter group describes that JAK-STAT, epidermal growth factor receptor (Egfr) and Wingless (Wg) signaling cooperatively regulate ISC self-renewal.[27] There are also conflicting publications about which cell types express Upd ligands under normal conditions. In one case, *upd* gene expression is below the limits of detection.[24] However, in other studies, Upd ligands are found to be expressed (1) broadly and variably in several cell types in the midgut epithelium,[23] (2) only in ISCs and EBs[25] or (3) only in the underlying visceral muscle.[26] Given the potent induction of *upd* in intestinal regeneration (see below), these discrepancies in *upd* expression under "homeostatic conditions" may be a result of bacterial load in the fly food of individual laboratories.[28] Thus, whether JAK-STAT activity is required for ISC self-renewal is not clear at present, and it may be necessary to establish defined conditions of sterility to study gut homeostasis in the absence of bacteria for reproducible results. Fortunately, all groups agree that hyper-activation of this pathway in ISCs under homeostatic conditions leads to increased ISC proliferation resulting in increased numbers of stem cells and their offspring.[23-26]

As mentioned above, the JAK-STAT pathway plays a critical role during regeneration of the intestinal epithelium. After injury with bleomycin, bacterial infection or physical injury, the rate of ISC proliferation is substantially higher.[24,28-35] Induction of Upd ligands, in particular Upd3, is common to all of these reports (**Fig. 2B**). A unifying model has emerged in which injured/dying ECs produce Upd cytokines, which then act non-cell-autonomously to induce proliferation in ISCs. Inactivation of the Hippo (Hpo) tumor suppressor pathway induces *upd*. Hpo represents a conserved tumor-suppressor pathway in which a serine-threonine kinase cascade negatively regulates the activity of the transcriptional co-activator Yorkie (Yki), the fly homolog of Yes-associated protein (YAP).[36] Yki promotes cell proliferation, growth and survival. Under homeostatic conditions, Hpo is active in ECs and restricts Yki to the cytoplasm. After injury or infection, Hpo becomes inactivated in ECs, leading to nuclear translocation of Yki, which induces directly or indirectly *upd*. Upd secreted from dying ECs activates STAT92E in ISCs, which increases proliferation.[32-35,37]

Ectopic activation of the Jun N-terminal kinase (JNK) stress pathway also leads to Yki activation and Upd ligand induction in EBs, ECs and EC-like cells.[24,32,34,38] Epistasis experiments place both Yki and JAK-STAT signaling downstream of JNK in ECs.[24,34] In addition, activated Yki may upregulate JAK-STAT signaling in ISCs, suggesting an autocrine loop in which ISCs produce Upd that then activates STAT92E in a cell autonomous manner.[32,33] By contrast, a study from the Jiang lab finds that Yki plays an autonomous role in ISC proliferation—but not via activation of STAT92E—and that Upd is induced only in ECs.[35] While Yki appears to be dispensable for autonomous ISC self-renewal under homeostatic conditions, ectopic activation of Yki within ISCs is sufficient to induce their proliferation.[32,33,35] The fact that Yki can induce Upd production in ISCs and that this augments ISC proliferation rate, suggests that Yki and STAT92E independently drive mitosis in ISCs.[33] Clearly there are numerous unresolved issues in the field. These include whether nuclear Yki is the primary activator of *upd* in the intestinal epithelium and whether JNK signaling can induce Upd independently of Yki.

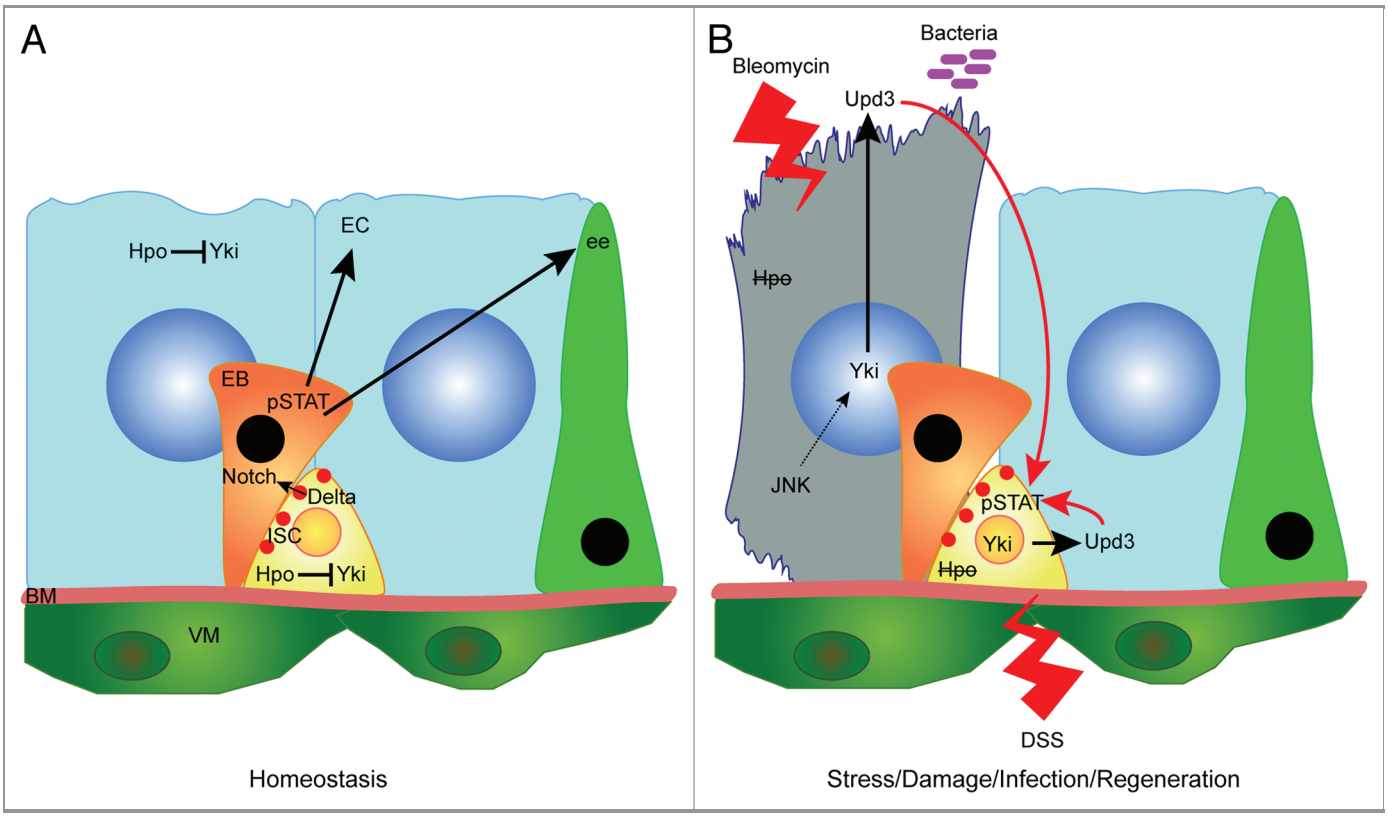


**Figure 2.** The adult midgut. (A) Homeostasis: absorptive polyploid enterocytes (ECs, blue) comprise the majority of the intestinal epithelium. Interspersed are hormone-producing enteroendocrine (ee) cells (green). Intestinal stem cells (ISCs) (yellow) are found close to the basement membrane (BM, red line). Visceral muscle cells (VM, dark green) reside under the basement membrane. ISCs express high levels of the Notch ligand Delta (red circles). Yorkie (Yki) activity is repressed in ISCs and ECs by the Hippo (Hpo) pathway. Notch signaling is prominent in enteroblasts (EBs, orange), the ISC daughter cell that gives rise to EC and ee cells. Activity of the JAK-STAT pathway (denoted pSTAT) is highest in EBs. STAT92E function is required in EBs for differentiation (arrows from pSTAT to EC and ee cells). Whether ISCs require JAK-STAT signaling for self-renewal is still controversial, as is the cellular source of *upd* (see text for details). (B) Regeneration: under a variety of conditions, including basement membrane damage (DSS), bacterial infection or bleomycin, ISC proliferation rate is dramatically increased as a regenerative response in the intestinal epithelium. In ECs, JNK signaling is activated while Hpo is inactivated. This leads to the nuclear accumulation of Yki, which directly or indirectly induces *upd* genes, in particular *upd3*. Upd ligands act non-cell-autonomously on ISCs and activate STAT92E (pSTAT) in these stem cells, which rapidly increases their proliferation rate. Upd can also be produced by ISCs, which then acts in an autocrine manner to stimulate ISC mitoses. Some groups have reported that Yki is activated in ISCs during regeneration and that this drives ISC proliferation in parallel to JAK-STAT signaling.

It should also be noted that Upd is not the only mitogen downstream of Yki, as EGFR ligands are also expressed in ECs after Hpo inactivation.[35] Consistent with the latter results, Staley and Irvine mention that knockdown of *STAT92E* only partially suppressed ISC proliferation caused by Hpo inactivation, indicating the existence of other stress-induced mitogens. Moreover, Wnt signaling is required for mitogenesis of ISCs under homeostatic conditions but is not induced in response to stress,[35,39,40] suggesting that stem cells can rely on different signals in normal and stress conditions.

## Hematopoiesis

A temperature-sensitive, gain-of-function mutation in the JAK *hop* [$hop^{Tumorous\text{-}lethal\ (Tum\text{-}l)}$] was actually the first to link the JAK-STAT pathway to hyper-proliferation of blood cells and cancer.[41] $hop^{Tum\text{-}l}$ animals display melanotic tumors at the permissive temperature and these tumors get larger when they are raised at the restrictive one.[42-44] These data suggest that the JAK-STAT pathway regulates the proliferation of hematopoietic stem or progenitor cells.

The JAK-STAT pathway plays important roles in larval hematopoiesis.[45,46] The lymph gland is the larval hematopoietic organ, which has three distinct zones in third instar larvae (**Fig. 3A**). Cells in the posterior signaling center (PSC) form the niche and secrete Upd3, Hedgehog (Hh) and Pvf1, which function to inhibit differentiation of progenitor cells (**Fig. 3B** and see refs. 45–47). It is controversial whether flies have HSCs. One group reported the existence of multipotent progenitors called prohemocytes that reside in the medullary zone (MZ),[48] whereas another group argues for the existence of fly HSCs.[49] Prohemocytes express the JAK-STAT receptor Dome, are quiescent and ultimately give rise to all Drosophila blood lineages.[48,50] Differentiation of hemocytes occurs in the cortical zone (CZ).[50] In addition, there is a pool of mitotic undifferentiated cells termed "intermediate progenitors" in the CZ that

maintains hemocyte numbers during the last larval stage.[48] Under homeostatic conditions, prohemocytes give rise primarily to plasmatocytes—phagocytic cells thought to be the functional equivalent of the mammalian myeloid lineage—and crystal cells, an insect-specific cell type that mediates melanization. Under immune challenge, for example infestation by parasitic wasps, prohemoctytes give rise to lamellocytes, an insect-specific lineage of large flat cells that encapsulate foreign objects too large to be phagocytosed.[44] Plasmatocytes constitute more than 90% of differentiated hemocytes, while crystal cells and lamellocytes make up less than 5%.

The Crozatier/Vincent lab showed that lymph glands from *STAT92E* temperature-sensitive animals reared at the restrictive temperature lose most if not all prohemocytes as a result of premature differentiation.[45] They proposed the model that Upd3 activates STAT92E in prohemocytes, and this maintains their quiescence (**Fig. 3B**). In the same issue of *Nature*, the Banerjee lab reported that Hh produced by the PSC activates Hh signaling in prohemocytes, again to keep these progenitors from differentiating.[47] Whether there is genetic interaction between JAK-STAT and Hh signaling in the lymph gland has not yet been reported. Furthermore, the FOG family member *u-shaped* (*ush*) represses prohemocyte differentiation, possibly through direct positive regulation of *ush* by STAT92E.[51] The regulation of a 150 bp *ush* enhancer by STAT92E was confirmed by mutation of the single putative STAT92E binding site, which results in loss of *ush* reporter expression in wild-type lymph glands. Whether expression of the wild-type *ush* enhancer is lost in *STAT92E* clones is not yet known. Nevertheless, these results do provide a potential mechanism through which JAK-STAT signaling promotes prohemocyte quiescence in a cell-autonomous manner.

Prohemocytes can be viewed as a reserve of progenitors that can rapidly differentiate into lamellocytes following infestation by the parasitic wasp *Leptopilina boulardi*, a natural predator of Drosophila larvae. Females of this wasp species oviposit into the hemocoel of second instar Drosophila larvae. Should the wasp egg hatch, it will use the Drosophila host as a food source. In this race for survival, prohemocytes quickly—within hours of wasp oviposition—differentiate and the lymph gland disintegrates. This response results in a tremendous increase in the number of circulating lamellocytes, which encapsulate the wasp egg and render it harmless.[44,52] After wasp infestation, *upd3* and *dome* transcripts are reduced while *et/lat* transcripts are increased.[5] This leads to a strong downregulation of JAK-STAT signaling in prohemocytes, allowing them to differentiate. In animals null for *et/lat*, the dramatic increase in lamellocytes after wasp parasitism is not observed and prohemocytes are not lost.[5] It should be noted that lymph glands from *et/lat* null mutant animals—which are adult viable and fertile—appear wild-type under homeostatic conditions. These data indicate that the role of *et/lat* is to switch off JAK-STAT signaling very rapidly in response to infestation.[5]

Activity of the JAK-STAT pathway is also required for appropriate hemocyte maturation. *STAT92E* clones are blocked in their differentiation to plasmatocytes.[53] However, crystal cell

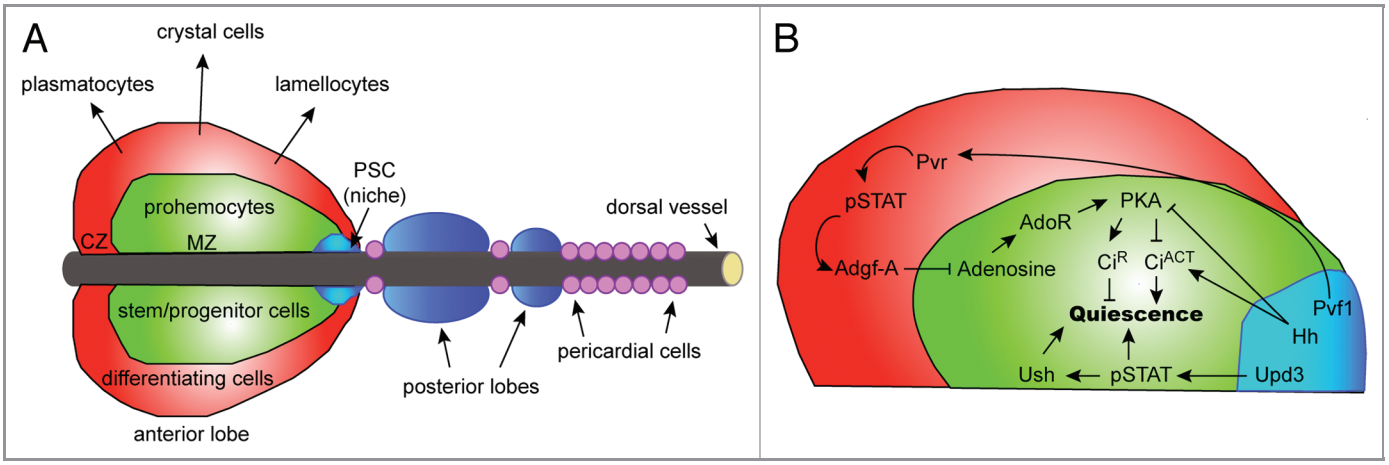


**Figure 3.** Hematopoiesis. (A) The lymph gland is the larval hematopoietic organ. In the third larval instar, one large anterior lobe and several smaller posterior lobes are found along the dorsal vessel, interspersed with pericardial cells. In the anterior lobe, there are three distinct zones. Cells in the posterior signaling center (PSC, blue) form the niche for multipotent progenitors called prohemocytes that reside in the medullary zone (MZ, green). Prohemocytes are quiescent and eventually give rise to all Drosophila blood lineages. Differentiation of hemocytes occurs in the cortical zone (CZ, red). Under homeostatic conditions, prohemocytes give rise primarily to plasmatocytes, which are phagocytic cells, and crystal cells, which mediate melanization reactions. Under immune challenge, prohemoctytes give rise to lamellocytes, large flat cells that encapsulate foreign objects. Plasmatocytes constitute more than 90% of differentiated hemocytes, while crystal cells and lamellocytes make up less than 5%. (B) Cells in the PSC (blue) produce soluble proteins like Upd3 and Hedgehog (Hh). Prohemocytes in the MZ (green) respond to Upd and Hh by activating JAK-STAT (pSTAT) and Hh signaling ($Ci^{ACT}$), respectively, which keeps these progenitors quiescent. PSC cells also produce Pvf1, which signals to cells in the CZ (red). Pvf1 activates Pvr on differentiating cells in the CZ, which leads directly or indirectly to activation of STAT92E (pSTAT) independently of canonical JAK-STAT signaling. Activated STAT92E increases expression of Adgf-A, a secreted protein. The primary function of Adgf-A is to inactivate extracellular adenosine, which can bind the adenosine receptor AdoR to activate PKA. By contrast, Hh signaling inhibits PKA. Since the level of PKA activity regulates whether $Ci^{ACT}$ is cleaved into a shorter repressor form ($Ci^{R}$), PKA is a node through which prohemocytes can be regulated to remain quiescent via Hh produced by the niche or a Pvr/STAT/Adgf-A cascade in CZ cells.

development appears to be unimpeded by the lack of *STAT92E*. Similar results were observed for loss-of-function mutations in *pannier* (*pnr*), which encodes a GATA transcription factor that is negatively regulated by Ush.[54] In fact, an enhancer trap that mirrors endogenous *pnr* expression is reduced in the lymph gland and brain in *STAT92E* loss-of-function clones, suggesting direct regulation of *pnr* by JAK-STAT signaling in hemocytes and perhaps other cell types.[53] Interestingly, *pnr* is actually negatively regulated by JAK-STAT signaling in the eye imaginal disc,[55,56] suggesting that the relationship between STAT92E and *pnr* is cell type-specific. In addition, lamellocytes were frequently seen in wild-type CZ cells at the borders of *STAT92E* clones. These results suggest that the JAK-STAT pathway normally regulates a signal to its neighbors to restrict their differentiation to lamellocytes.[53]

The Banerjee lab recently reported that Pvr, **P**DGF- and **V**EGF-**r**eceptor, is activated in CZ cells by Pvf1 produced in the PSC (**Fig. 3B**). Pvr binding to its receptor causes a STAT92E-dependent signaling cascade in CZ cells that regulates quiescence of prohemocytes in the MZ.[46] Transcriptional activity of STAT92E was observed in rare cells in the CZ that may correspond to intermediate progenitors. However, whether Pvr directly activates STAT92E was not addressed in this study. Activated STAT92E increases the expression of secreted adenosine deaminase growth factor-A (Adgf-A). The primary function of Adgf is to inactivate extracellular adenosine, which can bind the adenosine receptor AdoR to activate protein kinase A (PKA).[57] Hh signaling has the opposite effect on PKA; it inhibits PKA.[58] The level of PKA activity regulates whether the Cubitus interruptus (Ci) transcription factor that transduces the Hh signal is cleaved into a shorter repressor form $Ci^{R}$ or remains the longer active form $Ci^{ACT}$. As such, PKA is a node through which prohemocytes can be regulated to remain quiescent via Hh produced by the niche or a Pvr/STAT/Adgf-A cascade in CZ cells. Intriguingly, Pvr has also been shown to regulate proliferation in fly ISCs, suggesting a potential conserved link between Pvr and STAT92E in stem proliferation.[59]

Thus the emerging theme of the role of JAK-STAT signaling in hematopoietic progenitors is that this pathway must be switched off to permit differentiation.

## The Testis Stem Cell Niche

The Drosophila testis stem cell niche is a well-characterized system comprising a defined niche, called the hub, made up of post-mitotic cells, and two stem cell populations, germline stem cells (GSCs) and somatic cyst stem cells (CySCs) (**Fig. 4A**). GSCs can divide asymmetrically to self-renew and give rise to gonialblasts, which undergo four mitoses with incomplete cytokinesis before entering meiosis and maturing into sperm.[60] CySCs also divide asymmetrically, but their progeny, the cyst cells, are post-mitotic and envelop the developing germ cells while providing required support for their developmental progression.[61,62] The JAK-STAT ligand Upd is produced by hub cells and was thought until recently to be required for the self-renewal of both GSCs and CySCs (**Fig. 4B** and see refs. 63 and 64). However, the DiNardo lab has shown that activation of STAT92E only in the somatic lineage is sufficient for self-renewal of both stem cell populations[65] and that the requirement for STAT92E in GSCs is for their adhesion to the niche and not for self-renewal per se.[66] In fact, GSCs depend primarily on bone morphogenetic protein (BMP) signaling for their self-renewal, and BMP transcripts have been localized to hub and somatic cells.[67,68] Furthermore, sustained activation of the JAK-STAT pathway in CySCs causes BMP expression and expands both the CySC and GSC populations.[65,66,69] These data show that STAT92E coordinates the self-renewal of both stem cells via the CySC, by regulating self-renewal autonomously and by causing the expression of a secreted self-renewal factor that acts non-cell-autonomously on neighboring GSCs. The CySC is thus both a stem cell in its own right and, together with hub cells, forms an "extended" niche for GSCs.

It is not clear how STAT92E regulates adhesion in GSCs, but DE-cadherin levels are reduced within 16 h of *STAT92E* inactivation.[66] Moreover, STAT92E activity regulates cytoskeletal rearrangements in de-differentiating spermatogonia, a process in which spermatogonia revert to the GSC state and reoccupy an empty niche.[70,71] However, more is known of its role in CySC self-renewal. Two transcriptional targets of STAT92E have been identified, *zfh1* and *chinmo* (**Fig. 4B**). Both are required within CySCs for self-renewal, and both are functional effectors of STAT92E that act in a non-redundant manner in CySCs. Overexpression of either factor is sufficient to cause expansion of stem cell numbers, similar to STAT92E hyper-activation.[65,72] These data suggest that *STAT92E* and its targets *zfh1* and *chinmo* control expression of BMPs in CySCs, but whether this occurs directly or indirectly is not yet established.[66,72] Regardless, mis-expression of *upd* in the testis causes stem cell tumors comprised of GSCs and CySCs with only a single hub.[63,64] These results are most likely due to high STAT92E activation induced by Upd in CySCs, leading to increased BMP production, which acts to maintain the expanded germ cell population in a stem cell state.[65,66]

Another aspect of JAK-STAT signaling in the testis niche is that levels of pathway activity must be tightly regulated in order to maintain a functional homeostatic system, and both positive and negative regulators exist. In particular, *nurf301*, an ISWI-containing nucleosome remodeling factor, is required to maintain *STAT92E* expression in both GSCs and CySCs, presumably by ensuring that chromatin at the locus remains in an open state.[73] Conversely, the conserved feedback inhibitor of JAK-STAT signaling, *SOCS36E*, acts to keep STAT92E activity at least partially repressed.[4] There are normally 9–12 GSCs and approximately twice this number of CySCs in a wild-type testis. When *SOCS36E* is globally mutated, CySCs are able to outcompete GSCs for niche space, upsetting the usual balance between somatic and germline stem cells.[74] The "niche competition" phenotype observed in *SOCS36E* mutants was ascribed to increased STAT92E activation in CySCs, which then upregulated integrin-based adhesion and pushed out CySCs and GSCs. However, it should be noted that *SOCS36E* mutants are viable and fertile, indicating that although homeostasis is disturbed,

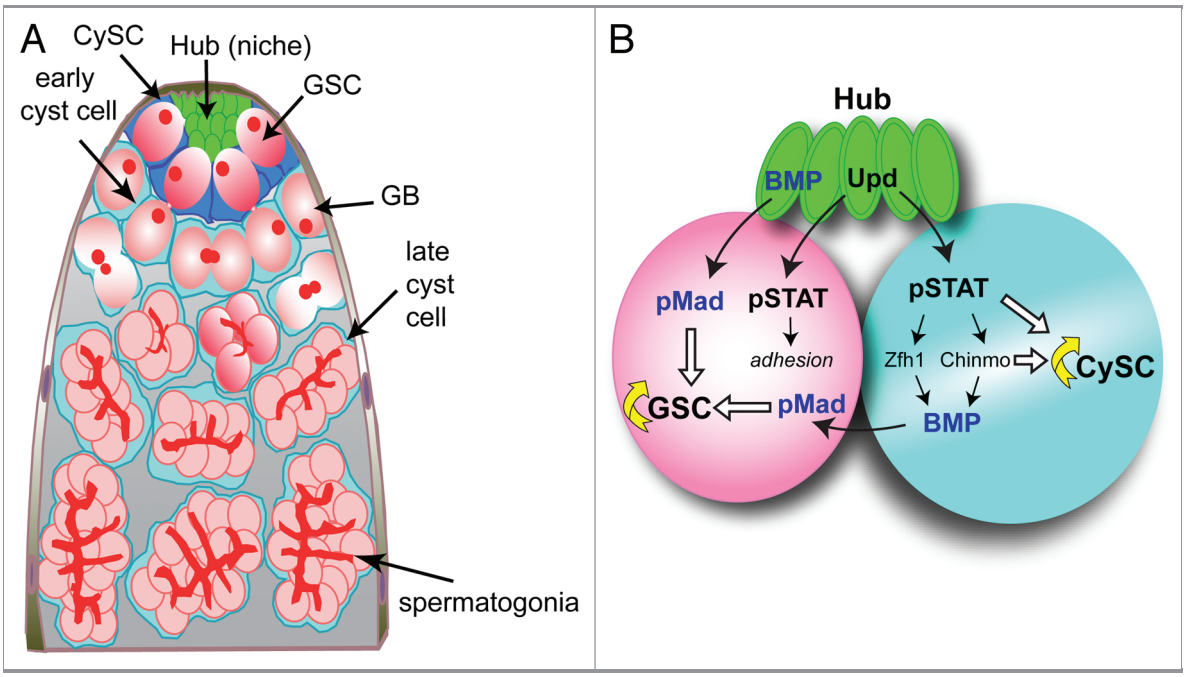


**Figure 4.** Testis stem cell niche. (A) Hub cells are post-mitotic and function as a niche to support two populations of stem cells, germline stem cells (GSCs) (pink/red) and cyst stem cells (CySCs) (dark blue). GSCs can divide asymmetrically to self-renew and give rise to gonialblasts (GB), which undergo four mitoses with incomplete cytokinesis to generate spermatogonia. CySCs also divide asymmetrically but their progeny, the cyst cells (light blue), are post-mitotic, and envelop the developing germ cells while providing required support for their developmental progression. (B) Hub cells secrete the JAK-STAT ligand Upd. STAT92E activation (pSTAT) is required for CySC self-renewal and for adhesion to the niche in GSCs but for not GSC self-renewal per se. The STAT92E target genes *zfh1* and *chinmo* are also required for CySC self-renewal. In addition, hub cells produce bone morphogenetic proteins (BMPs) and activation of BMP signaling in GSCs is required for their self-renewal. Furthermore, sustained activation of the JAK-STAT pathway or mis-expression of its targets *zfh1* and *chinmo* in CySCs causes BMP expression and expands both the CySC and GSC populations.

germ cell development is able to proceed relatively normally. The loss of GSCs observed in *SOCS36E* mutant animals[74] was unexpected because sustained activation of STAT92E in CySCs leads to expansion (not loss) of GSCs.[65]

A question that has not been addressed directly is how the diffusion and range of Upd is determined, as only the cells immediately contacting the hub display high levels of stabilized STAT92E protein.[65] It has been shown in the case of BMPs that the activity of receptors is limited to niche-stem cell synapses,[75] and that heparin sulfate proteoglycans (HSPGs), notably Dally-like, and extracellular matrix (ECM) proteins like Magu regulate the extent of BMP activity.[76,77] Moreover, Upd was first identified as a secreted heparin-binding glycoprotein tightly associated with the ECM,[78] suggesting a role for HSPGs in regulating JAK-STAT signaling in the testis niche. Another indication of the importance of regulating STAT92E levels is the correlation between diminishing Upd production in hub cells and the decrease in the number of GSCs that occurs with age. In fact, restoring Upd expression to older males can rescue the number of GSCs, underscoring the importance of JAK-STAT signaling to niche homeostasis in the testis.[79]

Previous work had also implicated JAK-STAT signaling in the maintenance of somatic escort stem cells, a supposed functional ortholog to CySCs in the ovary.[80] Ovaries from temperature-sensitive *STAT92E* animals reared at the restrictive temperature show a strong reduction in the number of GSCs, implicating STAT92E as a non-cell-autonomous regulator of female GSCs.[80] However, recent work has shown that escort stem cells are not actually stem cells, and therefore the role of STAT92E in this cell type awaits re-definition.[81,82] However, it is possible that the same genetic circuitry exists linking the somatic support cells to the maintenance of GSCs, as manipulations of escort cells can cause gain of GSCs through increased BMP signaling.[69,83] Thus, although escort cells are not a stem cell population, they may function to extend the GSC niche in the ovary, possibly through STAT92E and BMPs, in a manner reminiscent of the niche role of CySCs in the testis.

## Conclusions

In summary, these studies have revealed multiple roles of JAK-STAT signaling in Drosophila stem cells. We stress that to date only CySCs in the testis unequivocally require JAK-STAT pathway activity for self-renewal. By contrast, GSCs do not, and in these cells STAT92E is required for adhesive properties. Moreover, STAT92E signaling endows CySCs with the ability to form an "extended" niche for GSCs. While the role of JAK-STAT signaling in ISC self-renewal is not resolved, the pathway is critically involved in ISC expansion during regeneration. Therefore, we argue that the primary contribution of JAK-STAT signaling in ISCs is to induce a mitogenic response to stress. Conversely, in hematopoietic progenitors, the pathway is

required for quiescence and preventing differentiation. Finally, there is no over-arching theme to JAK-STAT function in stem cells in flies, reflecting the varied needs and cellular contexts of stem cells in different tissues.

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