Genetic alterations affecting the JAK-STAT signaling pathway are linked to several malignancies and hematological disorders in humans. Despite being one of the most extensively studied pathways, there remain many gaps to fill. JAK-STAT components are widely conserved during evolution. Here, we review the known roles of the JAK-STAT pathway in Drosophila immunity: controlling the different steps of hemopoiesis, both under physiological conditions and in response to immune challenge, and contributing to antiviral responses. We then summarize what is currently known about JAK-STAT signaling in renewal of the adult intestine, under physiological conditions or in response to ingestion of pathogenic bacteria.

Introduction

The Janus kinase–signal transducer and activator of transcription (JAK-STAT) signaling pathway was discovered from studies on the role of interferon in the control of immune responses in mammals. This pathway, which is highly conserved throughout evolution, transduces the activity of a variety of cytokines and growth factors in many important biological processes, such as embryonic development, hemopoiesis and immunity, and stem cell maintenance. Inappropriate JAK-STAT activation is linked to the development of several malignancies in humans, especially those derived from hematopoietic lineages, and to immunological disorders such as inflammatory disease, autoimmune disease, and allergy. Innate immunity, which is defined by its activation following pathogen recognition by germ-line encoded receptors, is the most ancient form of immune defense shared by all metazoans. Insects rely entirely on innate immunity for protection against external threats. The first, external protection against pathogens is the cuticle that constitutes a physical barrier, preventing microbe entry into the hemolymph (circulating body fluid). Overtaking this barrier generates two types of immune response, humoral and cellular. The humoral response, mediated by all metazoans. Insects rely entirely on innate immunity for protection against external threats. The first, external protection against pathogens is the cuticle that constitutes a physical barrier, preventing microbe entry into the hemolymph (circulating body fluid). Overtaking this barrier generates two types of immune response, humoral and cellular. The humoral response, mediated by all metazoans.

The JAK-STAT Signaling Pathway

JAKs and STATs mediate intracellular signaling in response to secreted type I cytokines. JAK tyrosine kinases are associated with the intracellular part of single pass transmembrane proteins that form homo- or heteromeric receptors. Ligand binding induces a conformational change that triggers pathway activation, via trans-phosphorylation of JAK molecules associated with the intracellular part of the receptor. Phosphorylated (activated) JAKs then phosphorylate the receptor, creating docking sites for STATs, and more than 30 different cytokines and growth factors in many important biological processes, such as embryonic development, hemopoiesis and immunity, and stem cell maintenance. Inappropriate JAK-STAT activation is linked to the development of several malignancies in humans, especially those derived from hematopoietic lineages, and to immunological disorders such as inflammatory disease, autoimmune disease, and allergy. Innate immunity, which is defined by its activation following pathogen recognition by germ-line encoded receptors, is the most ancient form of immune defense shared by all metazoans. Insects rely entirely on innate immunity for protection against external threats. The first, external protection against pathogens is the cuticle that constitutes a physical barrier, preventing microbe entry into the hemolymph (circulating body fluid). Overtaking this barrier generates two types of immune response, humoral and cellular. The humoral response, mediated by all metazoans.

The Toll and IMD signaling pathways and their downstream effectors, the NFκB like transcription factors Dif and Relish, respectively, control this process. The Toll and IMD pathways are homologous to the mammalian Toll-like receptor and tumor necrosis factor pathways, respectively. The initial discovery, in Drosophila, of the major role of Toll receptors/signaling in immunity, established this insect as a major model for the study of innate immune mechanisms. The cellular immune response is achieved by hemocytes responsible for phagocytosis of microbes, melanization, and encapsulation of large pathogens (for reviews see refs. 4 and 5). We review here the roles of JAK-STAT signaling in Drosophila immunity.

Keywords: Drosophila, lymph gland, wasp infection, hemopoiesis, gut
insect-specific reaction that contributes to wound healing; lamellocytes, corresponding to a cryptic, stress-induced cell fate, encapsulate foreign bodies too large to be phagocytosed, such as eggs laid in *Drosophila* larvae by parasitoid wasps.

Hematopoiesis occurs in two waves during development. First, a population of precursor cells for plasmatocytes and crystal cells is specified from the embryonic head mesoderm. Some of these cells differentiate before dispersing in the embryo, while others divide and differentiate later in circulation at the larval stage. A fraction of the embryonic hemocytes attach to the inner surface of the larval cuticle. Whether these “sessile” hemocytes, which can be mobilized upon immune challenge, perform specific functions remains unclear. A second population of plasmatocytes and crystal cells is released at the onset of metamorphosis, from a specific larval hematopoietic organ called the lymph gland (LG). Lamellocytes rarely differentiate under normal conditions but massively differentiate in the LG in response to wasp parasitism.

**Figure 1.** The JAK-STAT signaling pathway in *Drosophila melanogaster*. (A) Activation of JAK-STAT signaling. Binding of either cytokine, Unpaired (Upd1, 2, and 3), to the type I cytokine receptor Domeless activates trans-phosphorylation of the JAK kinase Hopscotch (Hop) and Dome phosphorylation, creating a docking site for STAT (Stat92E). Hop-phosphorylated STAT forms dimers which translocate into the nucleus and activate target genes via binding to TTCN (3–4)GAA sites. The green box in Dome corresponds to the cytokine binding domain (CBM), the blue box to a conserved region between Lat/Et and Dome (LDHR), the fibronectin III (Fn III) motifs are in red, the signal peptide in yellow and the intra-cytoplasmic region in gray. (B) Negative regulation of JAK-STAT signaling. Lat/Et acts as a dominant negative Dome co-receptor. Suppressor of cytokine signaling (SOCS) (Socs36E, Socs44A) prevents Stat92E recruitment onto the receptor. Protein inhibitors of activated STAT (PIAS) and PTP61F inhibit Stat92E function. Sumoylation of Stat92E has a repressive role in the regulation of the JAK-STAT pathway in *Drosophila*. BCL6 (Ken and Barbie, marked Ken) and NURF compete with Stat92E for binding to DNA.

**Drosophila** Hematopoiesis

Circulating hemocytes are the cellular component of the fly immune system. Three types of blood cells have been described in *Drosophila*: plasmatocytes, crystal cells, and lamellocytes. Plasmatocytes display phagocytic activity and represent functional equivalents of mammalian monocytes/macrophages; crystal cells are platelet-like cells involved in melanization, an insect-specific reaction that contributes to wound healing; lamellocytes, corresponding to a cryptic, stress-induced cell fate, encapsulate foreign bodies too large to be phagocytosed, such as eggs laid in *Drosophila* larvae by parasitoid wasps. *Drosophila* hematopoiesis occurs in two waves during development. First, a population of precursor cells for plasmatocytes and crystal cells is specified from the embryonic head mesoderm. Some of these cells differentiate before dispersing in the embryo, while others divide and differentiate later in circulation at the larval stage. A fraction of the embryonic hemocytes attach to the inner surface of the larval cuticle. Whether these “sessile” hemocytes, which can be mobilized upon immune challenge, perform specific functions remains unclear. A second population of plasmatocytes and crystal cells is released at the onset of metamorphosis, from a specific larval hematopoietic organ called the lymph gland (LG). Lamellocytes rarely differentiate under normal conditions but massively differentiate in the LG in response to wasp parasitism.
The circulating hemocyte population in pupae and adults thus consists of a mixture of hemocytes of both embryonic and larval origins. No hematopoietic organ has, so far, been identified in adult flies.

**JAK-STAT Signaling and STAT in the Larval Hematopoietic Organ, the Lymph Gland**

The larval lymph gland (LG) is specified from the embryonic cardiogenic mesoderm. At the end of embryogenesis the LG is composed of two lobes located on either side of the anterior portion of the heart, the aorta. Growth of these primary/anterior lobes during larval development is accompanied by the formation of more posterior, secondary lobes, although the cells/mechanisms at the origin of these secondary lobes remain unclear. In third instar larvae, while the posterior lobes contain only progenitor cells (called pro-hemocytes), three zones can be distinguished in each primary lobe: the medullary zone (MZ) composed of tightly packed pro-hemocytes, which are most akin to the common myeloid progenitor in mammals, the cortical zone (CZ) containing differentiating hemocytes and intermediate progenitors, and a group of about 20–30 cells at the posterior end of each lobe, forming the so-called posterior signaling center (PSC) (Fig. 2).

PSC cells were first identified in third instar larvae by their expression of the Notch ligand Serrate. They are specified in the embryo by the expression of the transcription factors Collier/Knot (Col), the Drosophila ortholog of mammalian early B-cell factor (EBF), and Antennapedia, a Hox protein. Two independent reports showed that the PSC plays a key role in third instar larvae, by maintaining the balance between multipotent pro-hemocytes in the MZ and hemocyte differentiation. This role is similar to that of the vertebrate hematopoietic niche in bone marrow, a cellular micro-environment, which controls self-renewal and differentiation of hematopoietic stem cells (HSCs). More specifically, the PSC cells were shown to express Hedgehog (Hh), which acts in a non-cell-autonomous manner to maintain the MZ. Since this founding work, it was shown that PSC cells are the source of several diffusible signals such as Wingless (Wg, a Wnt member) and Pvf1, one ligand of the platelet-derived growth factor (PDGF) signaling pathway, which, together with Hh, are necessary to maintain hemocyte homeostasis in the LG under normal conditions. The number of PSC cells is controlled by Dpp, a member of the TGF-β family of cytokines, together with Wg signaling, thus re-enforcing the parallels observed between the PSC and the vertebrate HSC niche (reviews in refs. 33–35). Finally, Spitz, one EGF-R ligand is released from the PSC in response to wasp parasitism and required for induction of lamellocyte differentiation. Important questions remain however to be addressed, such as the mechanism through which pro-hemocytes integrate the different PSC signals, or the role of the filopodial extensions emitted by PSC cells and which can contact MZ cells over several cell diameters (Fig. 2).

**Figure 2. JAK-STAT signaling and STAT functions in the Drosophila larval hematopoietic organ, the lymph gland.** (A) Confocal view of one primary lobe of the 3rd instar Drosophila lymph gland and (B) diagrammatic representation. Three zones can be distinguished, based on morphology and expression of specific markers: a small group of cells extending filopodia, the posterior signaling center (PSC, blue), the medullary zone (MZ, green) containing pro-hemocytes, and the cortical zone (CZ, red) containing differentiated hemocytes (plasmatocytes and crystal cells) and the intermediate progenitors (inner cortical zone, ICZ, orange). The cardiac tube (CT) is in gray. (C) Under normal conditions, Upd3 activates the JAK-STAT pathway in the MZ, and this is required to maintain a pool of pro-hemocytes. Binding of Pvf1 produced by the PSC to its receptor Pvr, in CZ cells, activates Stat92E expression. Stat92E is required non-cell autonomously in ICZ cells, and autonomously in CZ cells, for plasmatocyte differentiation. Stat92E also activates Adgf-A expression, leading to downregulation of Ado-R, which upregulates of PKA activity in the MZ. PKA activity, which contributes to the pro-hemocyte to hemocyte transition, is negatively regulated by Hh signaling from the PSC. (D) In response to wasp parasitism, there is a simultaneous decrease of Upd3 and Dome and increase of lat expression, leading to complete switching off of the JAK-STAT pathway in the MZ, a prerequisite to the massive differentiation of lamellocytes.

**JAK-STAT Signaling in Drosophila Hematopoiesis**

Beside their morphological aspect, hematopoietic progenitors in the MZ can be distinguished by their expression of GFP under the control of a Gal4 driver inserted in dome (Dome > GFP). In the embryonic mesoderm, JAK-STAT activity controls the expression of its own receptor, Dome, through binding of Stat92E to an enhancer called Dome-MESO. The Dome-MESO enhancer was cloned upstream of the LacZ reporter gene to generate transgenic lines, called dome-MESO-LacZ, with LacZ expression being used as a read out for JAK-STAT signaling. Overlap between high expression levels of Dome > GFP and dome-MESO-lacZ in MZ cells indicated that the JAK-STAT pathway is active in these cells. Loss of tep4 expression, a MZ marker, in Stat92E hypomorphic mutants, further showed that the JAK-STAT pathway is required in the LG for the maintenance of prohemocytes. Wasp parasitism induces disruption of
JAK-STAT signaling in the MZ and massive differentiation of pro-hemocytes into lamellocytes. \textit{lat} or \textit{lat\textsuperscript{et}}, the gene next to \textit{dome} on the X chromosome, encodes a Dome-related receptor with a truncated intracellular domain.\textsuperscript{48} Unlike \textit{dome}, \textit{lat} is neither expressed in embryos, nor required for fly viability and fertility. \textit{lat} is expressed, however, in larval MZ cells. While the absence of LG morphological defects in the \textit{lat} mutant indicates that the gene is not required for LG ontogeny or hemocyte homeostasis under physiological conditions, mutant larvae are unable to massively produce lamellocytes in response to wasp parasitism. Detailed analysis established that \textit{lat} is specifically required for switching off JAK-STAT signaling in the MZ following parasitism, thereby licensing pro-hemocytes to differentiate. In vivo and cell culture assays showed that Lat and Dome form inactive heteromers and that Lat antagonizes Dome activity in a dose-dependent manner. In response to wasp parasitism, there is an increase of the Lat/Dome ratio and a strong decrease in the \textit{upd3} mRNA level, leading to a complete inhibition of JAK-STAT signaling in the MZ that allows massive differentiation of lamellocytes (Fig. 2).\textsuperscript{43} Altogether, these data revealed the key role of JAK-STAT signaling regulation in mediating a dedicated cellular immune response in \textit{Drosophila}. The type I cytokine receptor family has considerably expanded in vertebrates,\textsuperscript{42} resulting both from an increased number of receptor genes and the generation of various protein isoforms, including truncated receptors that can act as co-receptors. Studies on IL13Ra2 or GP130/ GP130-like receptors in cell culture indeed suggested that short membrane-anchored receptors can behave as dominant-negative receptors.\textsuperscript{42,43} That Lat acts as a dominant-negative receptor rather than a co-receptor in \textit{Drosophila} is an in vivo example of the observations made in mammalian cell culture. Whether and when regulated expression of long and short receptor isoforms is employed in controlling specific aspects of vertebrate immunity, as it does in \textit{Drosophila}, remains to be investigated.

The \textit{col}, \textit{lat}, and \textit{Stat92E} mutant phenotypes indicate that JAK-STAT signaling is essential to preserving the pro-hemocyte status of cells in the MZ. This was rather unexpected, since constitutive activation of JAK-STAT signaling resulting from a dominant gain-of-function JAK mutation, \textit{hop\textsuperscript{Tum-l}}\textsuperscript{32}, a mutation first described 20 years ago, induces an overproliferation of circulating plasmatocytes and differentiation of lamellocytes in the absence of immune challenge, leading to the formation of melanotic masses in larvae and adult flies.\textsuperscript{34-46} A similar phenotype is observed upon ubiquitous expression of a constitutively active form of Stat92E, \textit{Stat92E\DeltaNc},\textsuperscript{47} consistent with high JAK-STAT activity being able to induce hemocyte differentiation. Accordingly, hemocytes located in the outer CZ and lacking Stat92E fail to undergo final differentiation into plasmatocytes\textsuperscript{42,48} (Fig. 2). Inhibition of \textit{Stat92E} in the inner CZ, which is enriched in intermediate progenitors,\textsuperscript{49} revealed an additional, non-cell autonomous role of Stat92E in preventing differentiation of surrounding cells into plasmatocytes. \textit{Stat92E} expression in CZ cells also contributes non-cell autonomously to the maintenance of the MZ. \textit{Stat92E} expression in these cells is dependent upon platelet-derived growth factor/vascular endothelial growth factor-like (PDGF/PVR) signaling. PDGF/PVR signaling is activated upon binding of Pvf1 (platelet-derived growth factor/vascular endothelial growth factor-like factor) that is produced by PSC cells and transported to differentiating hemocytes in the CZ. Thus, Pvf1/PVR signaling has been proposed to link Stat92E's CZ role in maintaining LG homeostasis to the PSC function.\textsuperscript{32}

One downstream target of both PDGF/PVR signaling and Stat92E in the CZ is Adenosine deaminase growth factor A (Adgf-A), whose function is to reduce the amount of extracellular adenosine. In the absence of Stat92E activity, adenosine is free to bind its receptor Ado-R, a seven pass trans-membrane domain receptor, is expressed in the MZ and signals through G proteins to activate adenylyl cyclase and protein kinase A (PKA). On the contrary, Hedgehog (Hh) signaling inhibits PKA activity. Hh signaling is activated in MZ cells upon reception of Hh secreted from the PSC, and it is required to maintain a pool of progenitors. PKA activity in the MZ is thus regulated positively by adenosine originating from the CZ\textsuperscript{32} and negatively by Hh signaling from the PSC\textsuperscript{30} (Fig. 2). The cross-talk between the PSC and the CZ that occurs at the level of PKA activity in the MZ is therefore responsible for maintaining the equilibrium between hemocyte differentiation and pro-hemocyte maintenance. In summary, JAK-STAT signaling plays several roles in the LG: it is required in the MZ for maintaining the multi-lineage capacity of pro-hemocytes; STAT, independent of JAK signaling, is required cell-autonomously for plasmatocyte differentiation; STAT in CZ cells contributes in a non-cell autonomous manner to hemocyte homeostasis. Many questions however remain open. First, the fact that the loss of JAK-STAT signaling in MZ cells leads to the loss of pro-hemocyte markers, but is not sufficient to induce their differentiation into mature hemocytes, suggests that JAK-STAT signaling is only one of several pathways contributing to maintain the progenitor state. Second, the mechanisms linking the loss of JAK-STAT signaling in pro-hemocytes and their exit from the MZ remain unknown. Third, the mechanisms by which high levels of JAK-STAT signaling enforce lamellocyte differentiation remain to be deciphered. While several screens for modifiers of JAK-STAT signaling have been performed, either in vivo, or in cultured cells, identification of JAK-STAT targets in hemocytes are not known.\textsuperscript{49-53} Finally, how \textit{Stat92E} acts in CZ cells, independent of JAK-STAT signaling remains to be established.

**The JAK-STAT Pathway in Circulating Hemocytes**

A role for JAK-STAT signaling in cellular immunity was first suggested by studies of the \textit{hop\textsuperscript{Tum-l}}\textsuperscript{32} mutant. It was observed early on that this mutation leads to an increased number of plasmatocytes and the massive differentiation of lamellocytes eager to encapsulate “self” tissue, leading to the formation of black masses/melanotic pseudo-tumors.\textsuperscript{49,54} A more recent study explored the role of JAK-STAT signaling in the interaction between hemocytes and tumors, generated in imaginal tissue by hyperactivation of Ras signaling.\textsuperscript{55} It showed that activation of Jun N-terminal kinase (JNK) signaling in tumors as well as in aseptic wounds, causes expression of JAK-STAT-activating cytokines from the injured tissue. Cytokine (mainly Upd3) production is amplified into a
systemic response, through the induction of additional cytokine production by the plasmatocytes that adhere to injured tissue (upon their detection of basement membrane disruption), eventually resulting in hemocyte proliferation. Activation of JAK-STAT signaling in hemocytes is thus required for their increased proliferation in response to both tumors and wounds. Basement membrane components are remarkably conserved throughout the animal kingdom, providing a unique structure for the immune system to sense tissue integrity. A similar innate reaction may thus underlie the response to tumors and tissue damage in vertebrates and humans. Secretion of JAK-STAT activating cytokines by hemocytes also regulates the humoral systemic response following a septic injury. The TumardotA (TotA) gene is upregulated in both hop <sup>−/−</sup> mutant flies and in response to bacterial infection. Its induction by septic injury is abolished in a hop loss of function mutant, showing that it requires JAK-STAT signaling. TotA protein subsequently found in the hemolymph, is mainly produced by the larval fat body. This indicates that stimulation of Upd3 expression in hemocytes in response to septic injury, activates the JAK-STAT pathway in fat body cells. Thus a global picture emerges with the circulating hemocytes as a central component in the regulation of Drosophila humoral and anti-tumoral responses. Signal(s) and the signaling pathway(s) involved in Upd3 upregulation in hemocytes remain to be identified.

**JAK-STAT in the Immune Response to Viral Infection**

Virus transmission and spread by insects is of major economical and public health importance. Viruses evolved diverse strategies to circumvent their host's antiviral defenses. Drosophila is a host to numerous viruses and a good model to study the mechanisms of antiviral defense. Current data point to the existence of two general mechanisms: RNAi inhibition of viral RNAs, such as the piwi-interacting (pi) pathway and an induced response calling on the expression of specific antiviral proteins. As in mammals, the induced response involves the activity of several signaling pathways, among which JAK-STAT signaling. Drosophila C virus (DCV), a picorna-like virus, which infects natural populations of *D. melanogaster*, is a classical model to study antiviral responses. Genome-wide profiling identified some 140 genes that are upregulated upon DCV infection. Several induced genes, including *virus-induced RNA 1 (vir-1)* contain STAT-binding sites in their promoter. Genetic analyses confirmed that hop and *Dome* activity is required for the induction of *vir-1* in response to DCV infection. Correlatively, hop mutant flies express low levels of *vir-1*, have high viral titers and succumb rapidly to DCV infection. Altogether, these data suggest a model in which DCV infected cells produce a cytokine that activates the JAK-STAT pathway and the immune defense in non-infected cells. An essential role of the JAK-STAT pathway in the antiviral response is also supported by the increased titers of SINV viruses after their inoculation into heterozygous STAT mutant flies. Of note, hop activity is required but not sufficient for the activation of some DCV-induced genes, indicating that additional regulation are needed. Moreover, microarray analyses of the *Drosophila* immune response to infection by different viruses (DCV, DXV, SIGMAV, FHV, and SINV), indicate that the response is virus-specific. Drosophila thus represents an excellent model to study the complexity of antiviral immune defenses.

**The JAK-STAT Pathway and Gut Regeneration**

The gut lumen of mammals and insects contains an abundant flora of resident, commensal bacteria. Two complementary effector mechanisms are essential to control infection by enteric bacteria in the *Drosophila* gut: generation of microbicidal reactive oxygen species (ROS) by intestinal cells leading to elimination of the ingested pathogenic bacteria, and local production of AMPs. Exposure to enteric pathogens can cause the loss of gut cells, as collateral effects of bacterial killing by ROS. Loss of gut cells, in turn, promotes intestinal stem cell (ISC) division and ISC-mediated epithelial repair, thereby maintaining gut homeostasis. Intestine epithelial renewal is an important aspect of the gut host defense. Infection of the *Drosophila* gut thus provides a powerful model to study the mechanistic links between the immune and repair pathways. The adult midgut, equivalent to the mammalian intestine, is composed of a single layer of specialized epithelial cells surrounded by a layer of visceral muscles. ISCs are scattered along the midgut and located basally, immediately adjacent to the basement membrane close to the visceral muscle. Under normal physiological conditions, homeostasis of the intestinal epithelium is maintained by the production of new cells by stem cell division. ISCs undergo asymmetric divisions throughout adult life, to giving rise to one cell that retains ISC properties and one transient progenitor, called an enteroblast (EB). EBs ultimately differentiate into either secretory endocrine cells (EEs) or absorptive enterocytes (ECs) depending on Notch signaling. Under physiological conditions, the JAK-STAT pathway is required for ISC proliferation and the differentiation of ECs. Low levels of JAK-STAT signaling are detected in ISCs and required to ensure their basal proliferation rate. The detection of Upd in visceral muscle cells indicated that Upd secreted by muscle cells could activate signaling in ISCs, but recent results suggest that Upd also controls ISC maintenance in an autocrine manner. The situation in response to stress conditions due to bacterial infection becomes more complex. Feeding flies with toxic compounds or invasive bacteria such as *Erwinia carotovora carotovora* or *Pseudomonas entomophila*, induces the rapid accumulation of ROS which, in turn, cause gut damage. Renewal of the damaged epithelium occurs through an increase of the ISC division rate. One recent model proposed that ROS-challenged enterocytes produce Upd3, and to a lesser extent Upd2 cytokines which activate the mitogenic activity of JAK-STAT signaling in ISCs, thereby increasing their division rate. Independent data confirmed Upd3 expression in ECs, but also in EBs, and suggested that ISC division in response to bacterial infection requires activation of JAK-STAT signaling in EBs and visceral muscles (VMs), but not in ISCs. In this scenario, it is the JAK-STAT stimulation of epidermal growth factor (EGF) production by EBs and VMS, which controls the rate of EGF-R-dependent ISC divisions. Finally, a recent study proposed
General Conclusion

The JAK-STAT pathway provides a simple membrane-to-nucleus mechanism to rapidly induce specific gene transcription and plays key roles in vertebrate immunity. Yet, despite 20 years of extensive studies, we are still surprisingly ignorant about this pathway’s tissue-specific functions and target genes. While the complexity of vertebrate immune responses is an obstacle to rapid progress, Drosophila has become a powerful genetic model to study the humoral and cellular aspects of innate immunity. Drosophila JAK and STAT are central players in both the genesis of immune cells and the fight against pathogens as diverse as viruses, bacteria and parasitic insects. Genetics, and genome-wide reverse-genetics and molecular screens, continue to reveal new components of the JAK-STAT pathway. Together with detailed studies of the cellular components of Drosophila immunity, they highlight the value of studying JAK-STAT signaling in Drosophila and its relevance to the understanding of JAK-STAT related human diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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References

1. Darnell JE Jr, Kerr IM, Stark GR. JAK-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science 1994; 264:1415-21; PMID:8197455; http://dx.doi.org/10.1126/science.8197455
2. Arbouzova NI, Zedde MP. JAK-STAT signalling in Drosophila: insights into conserved regulatory and cellular functions. Development 2006; 133:2605-16; PMID:16794301; http://dx.doi.org/10.1242/dev.02411
3. O’Shea JJ, Plenge R. JAK and STAT signaling mole- cules in immunoregulation and immune-mediated dis- ease. Immunology 2012; 136:542-50; PMID:22520847; http://dx.doi.org/10.1111/j.1365-2567.2012.03314.x
4. Lemaître B, Hoffmann J. The host defense of Drosophila melanogaster. Annu Rev Immunol 2007; 25:697-743; PMID:17202680; http://dx.doi.org/10.1146/annurev.immunol.25.022006.141615
5. Crozatier M, Meister D. Drosophila haematopoiesis. Cell Microbiol 2007; 9:1117-26; PMID:17394559; http://dx.doi.org/10.1111/j.1462-5822.2007.00930.x
6. Levy DE, Darnell JE Jr. Stat: transcriptional control and biological impact. Nat Rev Mol Cell Biol 2002; 3:651-62; PMID:12109125; http://dx.doi.org/10.1038/nrm909
7. Kwon SY, Xiao H, Glover BP, Tjian R, Wu C, Badenhorst D, Martinez-Agosto JA, et al. The Jak/STAT pathway is involved in synaptic plasticity. Neuron 2012; 73:374-90; PMID:22284190; http://dx.doi.org/10.1016/j.neuron.2011.11.018
8. Gough DJ, Shegal P, Levy DE. Nongenomic functions of STAT3. In: Jak-Stat signalling: from Basics to Disease, Decker T, Muller M, eds 2011.

We refer to the references listed in the provided text for detailed information on the topics discussed.
46. Luo H, Hantraty WP, Dearolf CR. An amino acid substitution in the Drosophila hopscotch Jak kinase causes leukemia-like hematopoietic defects. EMBO J 1995; 14:1412-20; PMID:7792418
47. Ekas LA, Cardozo TJ, Flaherty MS, McMullan EA, Gorovitzes FC, Bach EA. Characterization of a dominant-active STAT that promotes tumorigenesis in Drosophila. Dev Biol 2010; 344:621-36; PMID:20501334; http://dx.doi.org/10.1016/j.ydbio.2010.05.097
48. Minakhina S, Tan W, Seward R, JAK/STAT and the GATA factor Pannier control hemocyte maturation and differentiation in Drosophila. Dev Biol 2011; 352:308-16; PMID:21295688; http://dx.doi.org/10.1016/j.ydbio.2011.01.035
49. Flaherty MS, Zavadil J, Eckas LA, Bach EA. Genome-wide expression profiling in the Drosophila eye reveals unexpected repression of nos signaling by the JAK/STAT pathway. Dev Dyn 2009; 238:2235-53; PMID:19504457; http://dx.doi.org/10.1002/dvdy.21898
50. Flaherty MS, Salis P, Evans CJ, Eckas LA, Marouf A, Zavadil J, et al. chimino is a functional effector of the JAK/STAT pathway that regulates eye development, tumor formation, and stem cell self-renewal in Drosophila. Dev Cell 2010; 18:556-68; PMID:20404771; http://dx.doi.org/10.1016/j.devcel.2010.02.006
51. Mukherjee T, Schaefer U, Zeidler MP. Identification of JAK/STAT signaling components by genome-wide RNA interference. Nature 2005; 436:871-5; PMID:16094372; http://dx.doi.org/10.1038/nature03696
52. Baeg GH, Zhou R, Perrimon N. Genome-wide RNAi analysis of JAK/STAT signaling components in Drosophila. Genes Dev 2005; 19:1861-70; PMID:16595560; http://dx.doi.org/10.1101/gad.1320705
53. Hantary WP, Dearolf CR. The Drosophila Tumorous-lethal hematopoietic oncogene is a dominant mutation in the hopscotch locus. Mol Gen Genet 1993; 238:33-7; PMID:8479437
54. Pastor-Pareja JC, Wu M, Xu T. An innate immune response of blood cells to tumors and tissue damage in Drosophila. Dis Model Mech 2008; 1:151-9; PMID:19251400; http://dx.doi.org/10.1038/sj.wmbj.51.15.151
55. Beutler B, Eideneschek C, Grozot K, Imlel J, Takeuchi O, Hoffmann JA, et al. Genetic analysis of resistance to viral infection. Nat Rev Immunol 2007; 7:753-66; PMID:17893693; http://dx.doi.org/10.1038/nri2174
56. Wang JH, Valance S, Ramet M. Drosophila as a model for antiviral immunity. World J Biol Chem 2010; 1:151-9; PMID:20660684; http://dx.doi.org/10.1016/j.pnas.0913351017
57. Dongert C, Jouanguy E, Irving P, Troller L, Galliana-Arnoux D, Herzy G, et al. The JAK-STAT signaling pathway is required but not sufficient for the antiviral response of Drosophila. Nat Immunol 2005; 6:946-53; PMID:16086017; http://dx.doi.org/10.1038/nii1237
58. Auvadaul A, Veaster BR, Hardy GG, Kumar JP, Hardy RW. A novel system for the launch of alphaivirus RNA synthesis reveals a role for the lid path-way in arthropod antiviral response. PLoS Pathog 2009; 5:e1000582; PMID:19763182; http://dx.doi.org/10.1371/journal.ppat.1000582
59. Royet J. Ephemeral homeostasis and the underlying molecular mechanisms in the gut of the insect model Drosophila melanogaster. Cell Mol Life Sci 2011; 68:3651-60; PMID:21964927; http://dx.doi.org/10.1007/s00018-011-0828-x
60. Michieli CA, Perrimon N. Evidence that stem cells reside in the adult Drosophila midgut epithelium. Nature 2006; 439:475-9; PMID:16340959; http://dx.doi.org/10.1038/nature04371
61. Ohlstein B, Spradling A. The adult Drosophila posterior midgut is maintained by pluripotent stem cells. Nature 2006; 439:470-4; PMID:16340960; http://dx.doi.org/10.1038/nature04357
62. Takashima S, Mikrychyan M, Younossi-Hartenstein A, Merriam JR, Hartenstein V. The behaviour of Drosophila adult hindgut stem cells is controlled by Wnt and Hh signalling. Nature 2008; 454:651-5; PMID:18633350; http://dx.doi.org/10.1038/nature07185
63. Tzvetkova CV, Rosen E, Ojeda P, Chen X, Chen J, et al. The JAK/STAT signaling coordinates stem cell proliferation and multilineage differentiation in the Drosophila intestinal stem cell lineage. Dev Biol 2010; 338:28-37; PMID:19896379; http://dx.doi.org/10.1016/j.ydbio.2010.05.065
64. Jiang H, Patel PH, Kohlmaier A, Grenley MO, McEwen EA, Ando I, et al. A directed screen for genes involved in the adult Drosophila midgut. Genes Dev 2009; 23:1797-809; PMID:19773777; http://dx.doi.org/10.1101/gad.182709
65. Flaherty MS, Salis P, Evans CJ, Eckas LA, Marouf A, Zavadil J, et al. chimino is a functional effector of the JAK/STAT pathway that regulates eye development, tumor formation, and stem cell self-renewal in Drosophila. Dev Cell 2010; 18:556-68; PMID:20404771; http://dx.doi.org/10.1016/j.devcel.2010.02.006
66. Pastor-Pareja JC, Wu M, Xu T. An innate immune response of blood cells to tumors and tissue damage in Drosophila. Dis Model Mech 2008; 1:151-9; PMID:19251400; http://dx.doi.org/10.1038/sj.wmbj.51.15.151
67. Hantary WP, Dearolf CR. The Drosophila Tumorous-lethal hematopoietic oncogene is a dominant mutation in the hopscotch locus. Mol Gen Genet 1993; 238:33-7; PMID:8479437
68. Pastre-Paeria JC, Wu M, Xu T. An innate immune response of blood cells to tumors and tissue damage in Drosophila. Dis Model Mech 2008; 1:144-54; discussion 153; PMID:19048077; http://dx.doi.org/10.1242/dmm.0000950
69. Asha H, Nagy I, Kovacs G, Stetson D, Ando I, Dearolf CR. Analysis of Ras-induced overproliferation in Drosophila hematopoiesis. Genetics 2003; 163:203-15; PMID:12586708
70. Zettervall CJ, Anderl I, Williams MJ, Palmer R, Kurucz E, Ando I, et al. A directed screen for genes involved in Drosophila blood cell activation. Proc Natl Acad Sci U S A 2004; 101:14192-7; PMID:15388778; http://dx.doi.org/10.1073/pnas.0403789101
71. Sorrentino RP, Mielk JP, Govind S. Genetic analysis of contributions of dorsal group and JAK-Stat292E pathway genes to larval hematopoiesis, circulation and the egg encapsulation response in Drosophila. Genetics 2004; 166:1343-56; PMID:15082553; http://dx.doi.org/10.1534/genetics.166.3.1343
72. Hrusar T, Imler JL. Drosophila viruses and the study of antiviral host-defense. Adv Virus Res 2008; 72:227-65; PMID:19081493; http://dx.doi.org/10.1016/S0066-3527(08)00406-5