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Of blood cells and the nervous system

Hematopoiesis in the Drosophila larva

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Hematopoiesis is well-conserved between Drosophila and vertebrates. Similar as in vertebrates, the sites of hematopoiesis shift during Drosophila development. Blood cells (hemocytes) originate de novo during hematopoietic waves in the embryo and in the Drosophila lymph gland. In contrast, the hematopoietic wave in the larva is based on the colonization of resident hematopoietic sites by differentiated hemocytes that arise in the embryo, much like in vertebrates the colonization of peripheral tissues by primitive macrophages of the yolk sac, or the seeding of fetal liver, spleen and bone marrow by hematopoietic stem and progenitor cells. At the transition to the larval stage, Drosophila embryonic hemocytes retreat to hematopoietic "niches," i.e., segmentally repeated hematopoietic pockets of the larval body wall that are jointly shared with sensory neurons and other cells of the peripheral nervous system (PNS). Hemocytes rely on the PNS for their localization and survival, and are induced to proliferate in these microenvironments, expanding to form the larval hematopoietic system. In this process, differentiated hemocytes from the embryo resume proliferation and self-renew, omitting the need for an undifferentiated prohemocyte progenitor. Larval hematopoiesis is the first Drosophila model for blood cell colonization and niche support by the PNS. It suggests an interface where innocuous or noxious sensory inputs regulate blood cell homeostasis or immune responses. The system adds to the growing concept of nervous system dependence of hematopoietic microenvironments and organ stem cell niches, which is being uncovered across phyla.

Keywords: Drosophila larva, hematopoiesis, microenvironment, hemocyte, hematopoietic pocket, peripheral nervous system, sensory neuron, tissue macrophage, hematopoietic stem cell, niche

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Drosophila Blood Cell Lineages and Compartments

Drosophila blood cells, or hemocytes, play essential roles in the removal of apoptotic cells, immune responses against pathogens and parasites, and the repair of damaged tissue.[1-13] Three differentiated blood cell lineages, and undifferentiated prohemocytes that have progenitor function, are currently being distinguished.[13-19] Macrophages, also called plasmatocytes, correspond to the vertebrate myeloid lineage, and represent 90–95% of hemocytes at most developmental stages, serving roles in immunity and phagocytosis.[3,13,14,16] Invertebrate-specific crystal cells mediate melanization reactions in the embryo and larva,[13-16,20] and lamellocytes are induced by specific immune challenges in the larva to wrap large immune targets.[7,16,21-23] Several transcription factors and signaling pathways, many of which are conserved in vertebrates, play roles in the specification, differentiation, maintenance and functional responses of hemocytes.[18,20,22,24-49]

During development, Drosophila blood cells are supplied by a number of hematopoietic tissues to meet the demand during normal homeostasis and challenges such as infection, infestation or stress.[18,32,42] Each of these hematopoietic waves follows its own mechanisms, based either on the de novo generation of blood

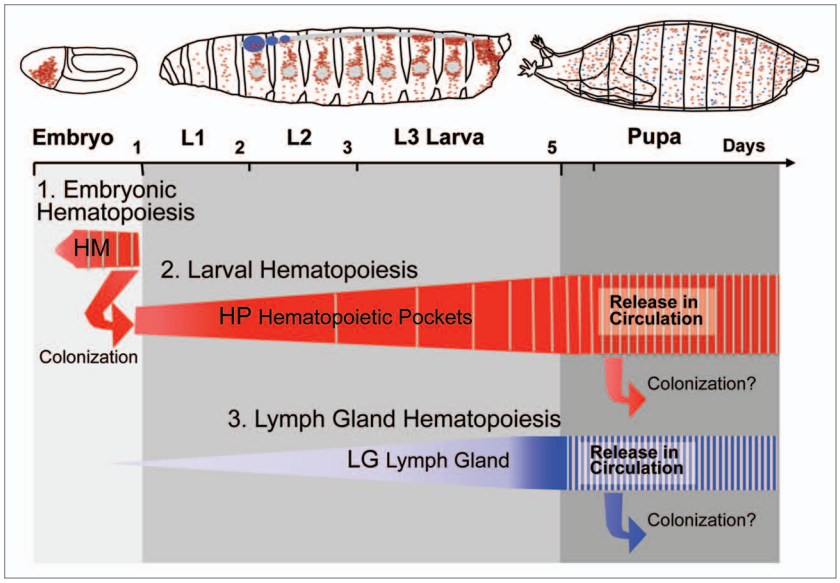

Figure 1. Hematopoietic waves in Drosophila. Timeline of hematopoietic waves in the Drosophila embryo and larva. Embryonic and lymph gland hematopoiesis are based on the de novo generation of blood cells, while larval hematopoiesis is founded by embryonic hemocytes that colonize hematopoietic pockets of the larval body wall. Vertical hatching indicates release of hemocytes from hematopoietic sites. Note progressive release of larval hemocytes into circulation over the course of larval development. HM, embryonic head mesoderm; HP, larval hematopoietic pockets; LG, lymph gland

cells, or the recruitment of existing blood cells by colonization of hematopoietic microenvironments.

Hematopoietic Waves Based on De Novo Blood Cell Generation

The initial wave of Drosophila hematopoiesis takes place in the embryo (**Fig. 1**). Hemocytes originate from the procephalic mesoderm, forming undifferentiated progenitor cells, or prohemocytes, which undergo a series of four rapid cell divisions during embryonic stages 8–11.[3,50] Subsequently, with the exception of about 5% of the cells that differentiate into crystal cells and retain proliferative capacity,[20] these cells stop proliferating and switch to a differentiation program, maturing toward plasmatocyte lineage.[3] As plasmatocytes differentiate, they disperse all over the embryo, migrating initially on defined paths.[8,10,51] Therefore, stage 11–16 embryos comprise a developmentally fixed number of 600–700 hemocytes, ~90% of which differentiate into plasmatocytes.[3,10,35]

An independent set of blood cells originates from the lymph gland (LG), which develops from an embryonic anlage that grows and matures over the course of larval development and supplies hemocytes at the beginning of metamorphosis,[7,13,16,52,53] corresponding to the third wave of hematopoiesis on the developmental timeline of Drosophila (**Fig. 1**). The LG is developmentally and physically associated with the dorsal vessel,[54] a circulatory organ with heart-like functions. LG and dorsal vessel arise from a common hemangioblast progenitor,[54] similar to the differentiation of hematopoietic and endothelial cells from a hemangioblast progenitor that emerges from the primitive streak during mammalian development.[55,56] The LG is organized into a central medulla of immature, tightly packed prohemocyte progenitors, a peripheral cortical zone of hemocytes that differentiate into plasmatocytes and crystal cells and show increased proliferation, and the posterior signaling center, a microenvironment that controls hemocyte progenitor maintenance and differentiation.[22,38,43,52,57] With the exception of severe immune challenges, LG hemocytes do not play roles in the immune or phagocytic functions in the larva,[16,22,53] but are released at the beginning of pupariation.[53] Thus, a separate set of "larval hemocytes" is active during larval development.[23,58]

Larval Hematopoiesis: A Wave of Macrophage Expansion Initiated by Blood Cell Colonization

Larval hematopoiesis fills the developmental gap between embryonic hematopoiesis and the release of LG hemocytes at the onset of metamorphosis (**Fig. 1**).[13,16,18,58] Only recently, larval hematopoiesis has been recognized to be initiated through the colonization of hematopoietic microenvironments by existing blood cells, rather than involving the de novo formation of prohemocytes or differentiation of existing progenitors, as was evidenced by extensive lineage tracing and functional approaches.[58] Differentiated hemocytes of the embryo are being carried over to the larval stage, colonize segmentally repeated epidermal-muscular (hematopoietic) pockets (**Fig. 2**) and proliferate in these locations,[58] explaining why embryonic hemocytes persist into postembryonic stages.[59] Interestingly, after a period of quiescence, and reduction in number in the late-stage embryo (You Bin Lin and K.B.),[3,16,58] these hemocytes re-enter, or proceed in, the cell cycle and expand from ~300 at the beginning of larval life to more than 5,000 in the third instar larva (You Bin Lin and K.B., unpublished).[16,58] While in early larval development most if not all, hemocytes retreat to hematopoietic pockets, an increasing number of hemocytes circulate in the hemolymph of second and third instar larvae, playing roles in immunosurveillance. Mobilization of hemocytes culminates during the prepupal phase, leaving only a small fraction of hemocytes in resident locations (K.M. and K.B., unpublished).[16,41] Throughout larval life, resident hemocytes are in a dynamic steady-state, exchanging between hematopoietic pockets.[58] Similar dynamics have been reported for circulating and dorsal vessel-associated larval hemocytes.[60,61] Resident hemocytes can be dispersed by mechanical manipulation, which is followed by their spontaneous return, or "homing," to hematopoietic pockets in an hour or less, suggesting that the microenvironment has attractive and/or specific adhesive properties.[58]

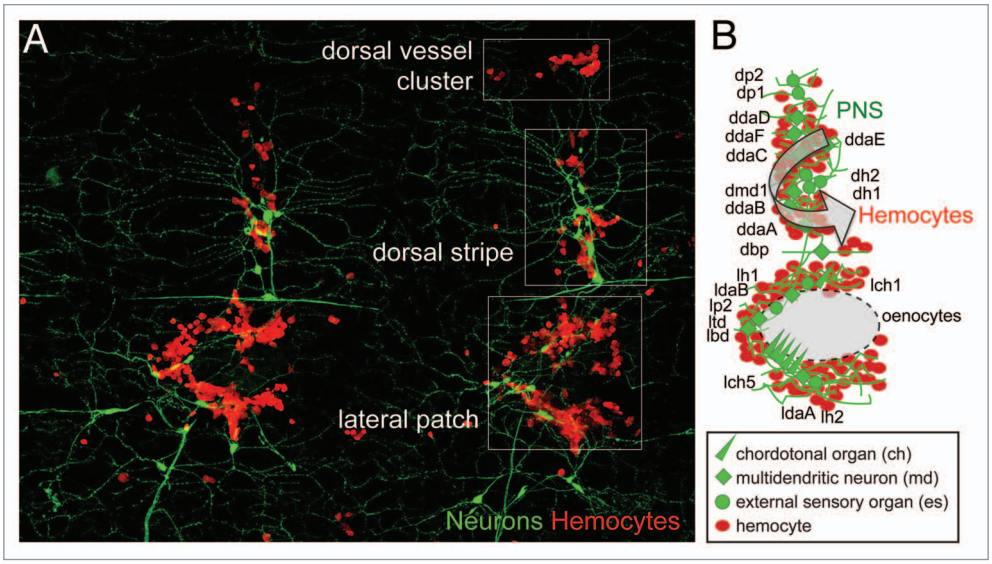

Figure 2. The PNS as hematopoietic microenvironment. (**A**) Co-labeling of neurons (*21–7-GAL4, UAS-CD8-GFP*, green),[63] and hemocytes (*HmlΔ-DsRed*, red),[58] located in the hematopoietic pockets of a filleted 3rd instar larva, anterior left, dorsal up. Two larval abdominal segments showing hemocytes colocalizing with the lateral and dorsal PNS clusters, forming the 'lateral patch' and 'dorsal stripe'. (**B**) Model of a lateral patch and dorsal stripe. Arrow represents attractive and inductive cues provided by cells of the PNS that support larval hemocytes.

The Nervous System as Microenvironment in Larval Hematopoiesis

Searching for the attractive and inductive constituents of the larval hematopoietic microenvironment, a central functional role of the peripheral nervous system (PNS), was identified.[58] The larval PNS consists of segmentally repeated ventral, lateral and dorsal neuron clusters, which sense intrinsic and environmental innocuous and noxious stimuli, such as mechanical strain and movement, temperature, chemicals and light.[62-66] Each segment contains a stereotyped cluster of chordotonal organs (ch), external sensory organs (es) and multidendritc neurons (md),[67] which extend dendritic processes into all areas of the larval body wall[68-70] and project axons ventrally to the brain.[69,71,72] Resident hemocytes tightly associate with the cell bodies and extensions of several neuron types in the lateral and dorsal PNS clusters, which jointly localize to hematopoietic pockets, forming the "lateral patch" and "dorsal stripe" of hemocytes (**Fig. 2**).[58] Lateral patches form around clusters of oenocytes, metabolically active cells with similarity to vertebrate hepatocytes,[73] which, however, are not essential for hemocyte attraction.[58] In contrast, larval hemocytes functionally depend on the PNS as attractive and trophic microenvironment: *Atonal (ato)* mutant,[74,75] or genetically neuron-ablated larvae, deficient for chordotonal organs and few md neurons, show a progressive apoptotic decline in hemocytes and an incomplete resident hemocyte pattern.[58] Complementary to this, supernumerary peripheral neurons induced by ectopic expression of the proneural gene *scute (sc)* can misdirect hemocytes to these ectopic locations.[58] Since the PNS contains several neuron populations that are distinct by function and lineage,[67,76,77] it will be interesting to dissect functional requirements and potential regulatory connections through neurons and/or their tightly associated glia or support cells.[78,79] Since the PNS has a prime function in detecting innocuous and noxious stimuli, and hemocytes become rapidly activated and mobilized for tissue repair and immune functions after an assault,[8,9,60,80,81] it is interesting to speculate that the anatomical and functional connection of the PNS with blood cells may coordinate developmental hematopoiesis, homeostasis and immune responses in the Drosophila larva. Similar mechanisms of blood cell colonization, and potentially regulation, could also play roles in post-larval hematopoiesis.

Parallels with Mammalian Systems

Hematopoiesis in the Drosophila larva and vertebrates show numerous parallels. In vertebrates, seeding of hematopoietic sites through colonization by blood cells occurs at multiple times during development. Primitive macrophages of the yolk sac give rise to many types of tissue macrophages, such as the microglia of the brain,[82-85] dendritic cells of the skin, Kupffer cells of the liver and resident macrophages of the pancreas, lung, spleen and kidney,[86] and also differentiated blood cells from other sources, such as monocytes from fetal liver, seed certain tissue macrophage populations.[87] Similarly, AGM (aorta gonad mesonephros) -derived hematopoietic stem cells (HSCs) engraft the fetal liver, and, later on, the thymus, spleen and bone marrow,[88-90] and committed T-cell progenitors from the thymus seed primary lymphoid organs such as the gut.[91]

Blood cells that give rise to a hematopoietic population typically require an appropriate microenvironment, or niche, which provides signals that ensure their survival, maintenance, controlled proliferation and differentiation. For example, the mammalian bone marrow niche relies on sympathetic nerves and their associated

glia, mesenchymal stem cells and many other cell types that contribute to the hematopoietic microenvironment.[92-96] Likewise, tissue macrophages are attracted to and maintained by specific microenvironments,[84,86,97-102] and peripheral niches attract and support hematopoietic stem and progenitor cells in tissue repair, revascularization and tumorigenesis.[96,103,104] During development and in adulthood, murine hematopoietic stem and progenitor cells cycle between resident hematopoietic sites, peripheral blood and other tissues.[89,105] Egress and homing are governed by various signaling systems including G-CSF/G-CSFR, CXCL12/CXCR4 and -7, Slit2/Robo4 and Sphingosine 1-phosphate/S1P receptor.[92,103,104,106-109]

The peripheral nervous system (PNS) is an essential part of the microenvironment in a variety of vertebrate target tissues, including hematopoietic and immune organs,[93,110-112] liver[113] and endocrine pancreas.[114,115] In the vertebrate bone marrow, sympathetic nerves and their associated glia regulate hematopoietic stem cell (HSC) localization, proliferation and maintenance.[93,94,110,111,116,117] Communication takes place through direct stimulation of β-adrenergic and dopaminergic receptors on HSCs[117] and indirectly, through sympathetic β-adrenergic signals that suppress stromal cells of the bone marrow niche to engage in CXCL12/CXCR4 signaling with HSCs.[93,110] Further, glia of the PNS also play important roles, mediating localized activation of TGF-β that promotes HSC maintenance.[94,95] Immune responses in lymphocytes and myeloid cells may be regulated via direct contacts with nerve terminals,[112,118,119] and neural regulation also governs immune responses in *C. elegans*,[120,121] providing further support that PNS microenvironments in the immune system and hematopoietic sites are widely conserved across phyla. Besides such local regulation by the PNS, hematopoiesis and immunity are further regulated by systemic signals from the central nervous system and, in vertebrates, the hypothalamic-pituitary-adrenal axis.[48,122-125]

Drosophila larval hematopoiesis sheds a new evolutionary perspective on the two myeloid systems in vertebrates, i.e., myeloid cells that derive from HSCs and the self-renewing tissue macrophages.[82,86,84,87] Much like Drosophila larval hemocytes, vertebrate tissue macrophages expand within local microenvironments.[82,84,86,97,99] However, compared with the systemic functions of Drosophila larval hemocytes,[16,23,60] vertebrate tissue macrophages may have evolved to adopt more restricted, tissue-specific roles.[126-128]

Outlook

The optically transparent and genetically tractable Drosophila larva provides a powerful system to study principles of nervous system-hematopoietic regulation. Drosophila sensory neurons comprise a major part of the larval hematopoietic niche, suggesting an interface that could link innocuous or noxious stimuli with blood cell homeostasis and immune responses. It will be interesting to investigate further whether, in vertebrates, sensory innervation in the proximity of tissue macrophages[129] and in microenvironments of HSCs in the bone marrow and lymph nodes[118,119,130] serve similar functions.

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