

# Drosophila hematopoiesis : a model system to decipher niche function *in vivo*.

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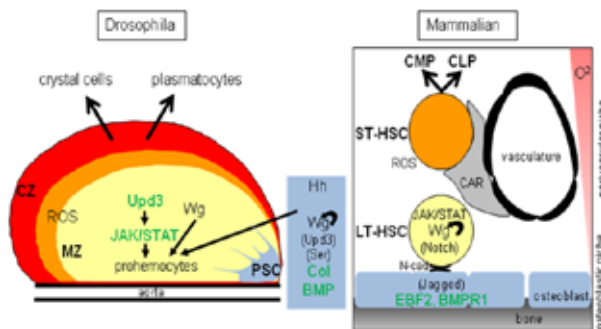


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## Drosophila hematopoiesis : a model system to decipher niche function *in vivo*

Vertebrate hematopoietic stem cells (HSCs) in the bone marrow ensure continuous blood cell production throughout adulthood. Renewal of HSCs is controlled by extrinsic cues provided by the niche, but how this occurs remains largely unknown. The *Drosophila* larval hematopoietic organ, the lymph gland (LG) is a good model to study *in vivo* niche functions. A cluster of cells, called the Posterior Signaling Centre (PSC), acts as a niche to control the balance between the maintenance of hematopoietic progenitors and their differentiation into specialised blood cells (hemocytes). In the course of this programme, we established hemocyte lineages in the LG and discovered a new mode of regulation of the JAK/STAT pathway, by a short non signaling receptor. Transcriptome analyses of dissected LGs allowed us to identify new genes expressed in this organ and establish that activation of the Dpp/BMP pathway in PSC cells controls the niche size. In absence of Dpp signaling, the number of PSC cells increases, resulting in a lack of hemocyte differentiation. Altogether, these data allow new parallels to be drawn between mammals and *Drosophila* for hematopoietic niche maintenance and function.



**Figure 1. The parallels between hematopoiesis in the *Drosophila* lymph gland and the mammalian bone marrow.** Left panel: The primary lobe of the lymph gland, at the origin of three types of hemocytes, comprises the PSC (blue), the Medullary Zone (MZ, yellow) containing prohemocytes/progenitors, intermediate progenitors (orange) and the Cortical Zone where hemocyte differentiation takes place (CZ, red). Signaling pathways active in the PSC and MZ are indicated. The novel data obtained in our ANR program are indicated in green. Right panel: Schematic representation of the quiescent, long-term (LT) and primed/activated, short-term (ST) HSCs and their niches in the mammalian bone marrow. Common lymphoid and myeloid precursors are indicated as CLP and CMP, respectively. Signaling pathways involved in the communication between HSCs and their niches are indicated. EBF2 is the mammalian Col ortholog and BMP1A is one BMP receptor; both are required in osteoblasts to control LT-HSCs.

## Major results

Our results indicate that the fate restriction between two type of hemocytes, is established very early during larval development and reveal the existence of intermediate hematopoietic progenitors. A dominant negative receptor plays a key role in switching off JAK-STAT signaling in response to wasp parasitism. Dpp/BMP signaling activity in the PSC is required to maintain a low number of PSC cells, via the repression of the proto-oncogene *dmyc*. The tight control of the PSC cell number is crucial for maintaining the balance between precursors and differentiated hemocytes

## Scientific production

Characterisation of hemocyte lineage and PSC function: **Krzemien et al. (2010) Dev. Biol.** ;**Krzemien et al. (2010) Int. J. Dev. Biol.**; **Vincent et Crozatier (2010) J. Mol. Cell Biol.**  
Deciphering the regulation of the JAK-STAT signalling in controlling the immune response: **Makki et al., (2010) PLoS Biol**; **Crozatier et Vincent, (2011) DMM**  
Role of the BMP pathway in controlling the niche size: **(Pennetier et al., submitted)**  
Identification of new genes expressed in LGs: **(Oyallon et al., in prep)**

## Conclusions -Perspectives

The establishment of a large set of data describing gene expression in the PSC (niche) and pro-hemocytes is a central result of our project. This constitutes the basis for both deciphering molecular networks involved in maintaining a functional niche and characterizing, at the molecular level, cellular communications involved in the control of *Drosophila* hematopoiesis. Altogether, this provides important new knowledge on a primary aspect of innate immunity that controls of quiescence/proliferation of hematopoietic progenitors in physiological conditions and in response to specific immune threats. Our starting point for studying hematopoiesis and hemocyte homeostasis was the finding that Col, the *Drosophila* ortholog of mammalian EBF (Early B-Cell factor), was required to specify the hematopoietic niche. The recent report that EBF2 acts as a transcriptional determinant of the osteoblastic niche that regulates the maintenance of HSC in mice (Kieslinger et al., 2010), underlines striking new parallels between flies and mammals. Integration of our transcriptome data sets with those obtained from mouse osteoblasts, is expected to provide important new fundamental knowledge on the conservation of molecular and cellular regulations involved in the control of hematopoiesis throughout metazoan evolution

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