A fly's view of the hematopoietic niche

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The hematopoietic system is a highly complex and extremely active organ that produces approximately 10^8 white blood cells, with very different characteristics, every hour of the day.[1] In order to do this for the entire life of a human being, the system must also maintain the undifferentiated hematopoietic stem cells (HSCs) that are the source of all the differentiated blood cells. As always in multi-cellular organisms, blood cells are not separated from the rest of the body and the other cell types, and interactions between the blood cells and other cells are extremely important to maintain the HSC population. This typically occurs in the so-called 'hematopoietic stem cell niche' where HSCs interact with various other cells, receive signals through soluble molecules, shear stress, oxygen tension and temperature.[1,2,3] In the past years, several new cell types have been identified that determine the fate of HSCs, including perivascular mesenchymal stem cells and non-myelinating Schwann cells (glial cells).[4,5] Moreover, it was recently demonstrated that deregulation of the niche has not only an impact on the maintenance of HSCs, but can even induce myelodysplasia and acute myeloid leukemia.[6]

In a recent study by Mondal and colleagues,[7] a new signaling component between differentiating cells and progenitor cells was identified in the hematopoietic niche of the fruitfly *Drosophila melanogaster*. The hematopoietic cells of drosophila, the hemocytes, develop within the lymph gland where differentiating blood cells, the progenitor cells and the cells of the microenvironment (the niche) are all found together. In this system, the niche cells produce Hedgehog ligand. This binds on the progenitor cells where it activates Hedgehog signaling which is required for the maintenance of the progenitor cells. Unexpectedly, the authors found that knock-down of adenosine deaminase growth factor-A (Adgf-A) in the differentiated blood cells, induced loss of quiescence of the progenitor cells. Adgf-A is a secreted enzyme (similar to vertebrate adenosine deaminase, for example, produced by monocytes) that is produced by the differentiated blood cells. Furthermore, this study also identified signals from the niche cells (Pvf ligand, related to PDGF/VEGF in vertabrates) and additional signaling in the differentiated blood cells (Pvr receptor, related to PDGF/VEGF receptors, as well as STAT signaling) to be required for the maintenance of the progenitor cells. These signals in drosophila are related to the known role of effects of the hematopoietic niche on hematopoietic stem and progenitor cells in vertebrate cells,[1,3] but effects of the differentiated blood cells such as the Adgf-A described by Mondal and colleagues, is a new player in this process. Mondal *et al.* elegantly demonstrate that not only signals from the niche cells but also signals from the differentiated blood cells are required to regulate the correct number of blood cells and their maintenance.

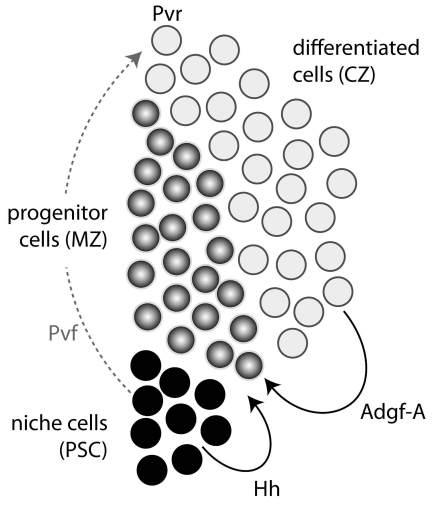

Figure 1. Schematic overview of the hematopoietic niche in the fruitfly. Niche cells (in the Posterior Signaling Center, PSC) produce Hedgehog ligand (Hh) and Pvf ligand. Pvf acts mainly on the Pvr receptor on the differentiated blood cells in the Cortical Zone (CZ), while Hh acts on the progenitor cells (in the Medullary Zone, MZ). In addition, the progenitors also receive a signal from the differentiated cells, through Adgf-A. Both the Hh and Adgf-A signals are important for the maintenance and quiesence of the progenitor cells.

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