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Title:	Understanding the molecular and genetic basis of hematopoietic niche regulation by differentiating blood cells in the developing larval lymph gland of Drosophila melanogaster
Authors:	Budakoti, Prerna (/jspui/browse?type=author&value=Budakoti%2C+Prerna)
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Abstract:	Stem cell niches play a fundamental role in maintaining the homeostasis between maintenance and differentiation of stem/progenitor cells. Although we understand the diverse mechanisms underlying the regulation of stem/progenitor cells by their niches, we are just beginning to appreciate the role of stem/progenitor cells and differentiated cells in shaping the niche architecture and maintaining niche function during development and disease. Understanding the intricacies of stem cell niche regulation is crucial for engineering artificial stem cell niches, a prerequisite for future regenerative medicine and therapeutic discoveries. In the recent past, the larval hematopoietic organ of Drosophila, commonly known as the lymph gland, has emerged as a fantastic model to address several aspects of blood cell development and homeostasis for its simple blood cell lineage and its developmental and functional parallels with the vertebrates. Most of the evidence stems from the analyses of the primary lobe of the multi- lobed lymph gland. Our study reveals that during normal development, the proliferation of the hematopoietic niche cells is non-autonomously regulated by differentiating blood cells in the primary lobe of the lymph gland of Drosophila. We demonstrate that activation of JAK-STAT signaling induces ldh expression in differentiating blood cells. A gradual increase in Ldh activity leads to the production of elevated levels of lactate in these cells. Lactate released by differentiating blood cells, in turn, contributes to restricting the proliferation of niche cells by potentiating Dpp/BMP signaling. Genetic manipulation of any member of the signaling cascade that either alters the production and release of lactate from differentiating blood cells or restricts lactate entry in the niche cells leads to the loss of this control. Quite intriguingly, differentiating blood cells ectopically expressing the human oncogenic chimeric protein AML1-ETO, responsible for causing leukemia, also harness this developmental regulatory mechanism to subjugate niche cell proliferation. Restricting the niche size by augmenting this pathway might be a contributing factor that favors a prolific increase of the AML1-ETO expressing differentiating blood cells. Thus, by unraveling an unknown paradigm of a cytokine-mediated and metabolite-dependent regulation employed by differentiating blood cells to restrict niche cell proliferation, our research establishes lactate as a regulator of hematopoietic niche functionality during development and disease.
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