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Title:	Role of extrinsic and intrinsic factors in regulation of the hematopoietic niche
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Abstract:	Hematopoiesis is the developmental process of the formation of blood cells. In both vertebrates and the well studied model organism Drosophila melanogaster, hematopoiesis takes place in two waves; primitive and definitive hematopoiesis. Definitive hematopoiesis in Drosophila takes place in a specialized organ known as the lymph gland, and shares several similarities with vertebrate definitive hematopoiesis in the aorta-gonad-mesonephros region, making Drosophila an excellent model to study hematopoiesis and related morbidities. The lymph gland houses mainly three types of cells, each occupying a distinct domain of the lymph gland, dividing the lymph gland into distinct zones. The differentiating blood cells form the outermost layer and constitute the cortical zone, the progenitor cells are found inner to the cortical zone and constitute the medullary zone and the niche cells located in the innermost region constitute the posterior signaling centre. The various zones of the lymph gland are known to cross talk with each other for the maintenance of the progenitor population. But, a signal from the differentiating cells to the niche has not been found. Here, we show that Upd2, a ligand of the JAK-STAT signaling pathway is produced by the differentiating cells and is crucial for the maintenance of the niche cell population. Upd2 activates the canonical JAK-STAT pathway, leading to the activation of STAT92E in the medullary and intermediate zones. Loss of Upd2 results in an increased proliferation of the niche, along with precocious differentiation in the medullary zone. We also show that this deregulation of niche cell homeostasis is at least in part due to an upregulated insulin signaling coupled with a downregulation in Dpp signaling. This is the first report of a cytokine molecule regulating insulin signaling in the lymph gland. Upon loss of Upd2 expression, the niche cells downregulate the expression of Hedgehog, a molecule known to be involved in progenitor maintenance. We conclude that downregulated Hedgehog expression contributes to the precocious differentiation of the progenitor population. We also show that overexpressing STAT92E in the differentiating cells, although leads to a decrease in progenitor index and overall lymph gland size, does not affect the niche cell population. Our study throws light on the role of JAK-STAT signaling in maintaining the hematopoietic niche, and consequently overall hematopoiesis in the lymph gland. The high degree of conservation in hematopoietic processes between Drosophila and humans means that building on our results could give us a better understanding of the role of JAK-STAT signaling in hematopoietic malignancies in humans that arise due to misregulation of JAK-STAT signaling.
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