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Insulin signaling and its role in *Drosophila* midgut homeostasis

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Insulin receptor signaling plays an essential role in mediating cellular processes in response to organismal nutritional status. It does not only promote growth and metabolism but is also involved in regulating cell proliferation. So far many epidemiological studies proved a strong association between hyperinsulinemia (e.g. in obese or diabetic patients) and the formation of various human malignancies as breast, lung, prostate and colorectal cancer, demonstrating a crucial role for Insulin signaling in carcinogenesis. Since intestinal stem cells themselves are prime suspects for the source of colorectal carcinogenesis further studies on the impact of Insulin receptor signaling on intestinal stem cells and intestinal homeostasis will hopefully provide new insights into stem cell biology and pre-stages of carcinogenesis. Thus a better understanding of this complex system will help to further develop novel approaches to diagnose and treat several human malignant tumors, especially colorectal cancer.
Due to high evolutionary conversion between *Drosophila* and mammals as well as various intriguing genetic techniques, in the present study *Drosophila melanogaster* served as a perfect model system to investigate the role of intestinal stem cell regulation and Insulin receptor signaling. As the results of this thesis indicate, Insulin receptor signaling plays an important role in intestinal homeostasis and stem cell regulation. On the one hand it drives intestinal stem cell (ISC) proliferation and promotes growth and endoreplication of differentiating enteroblasts and on the other hand it is required for regeneration after bacterial infection. Furthermore two Insulin receptor ligands, dILP3 and dILP6, are expressed in the adult midgut itself, acting as a local source to modulate Insulin signaling. These findings highlight a functional role of intestinal Insulin receptor signaling and demonstrate its requirement for regular regeneration. Further experiments revealed that Insulin receptor overexpression drives ISC proliferation not only due to its own mitogenic potential but also due to cell non-autonomous effects. Insulin receptor overexpression drives excessive growth and endoreplication of differentiating cells that results in enlarged enterocytes. These lead to

tissue disruption and thereby initiate a regenerative response that further promotes ISC proliferation. Hence major signaling pathways that regulate intestinal homeostasis are cooperatively involved in this complex signaling machinery, namely the JAK/STAT, JNK and EGFR signaling pathway. This study highlights the non-autonomous contribution of these signaling activities to Insulin receptor overexpression and thus points out the relation between Insulin receptor signaling and other oncogenic signaling pathways. In terms of carcinogenesis it may shed further light on the complex signaling machinery that follows intestinal Insulin receptor signaling due to non-autonomous effects promoted by excessive growth.