Abstract

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Animal growth is a complex process that is intimately linked to the developmental program in order to form fit adults with proper size and proportions. Genetics is an important determinant of growth, exemplified by the role of local diffusible molecules in setting organ proportions for a given species. In addition to this genetic control, organisms use adaptation mechanisms allowing modulating the size of individuals according to environmental cues, among which nutrition. Therefore, sophisticated cross-talks between local and global cues are at play for the determination of the final size of an individual. The objective of our work is to tackle the mechanisms involved in coupling growth control with environmental cues, as well as the mechanisms participating in growth arrest and the determination of final size. We use a blend of physiological and genetic approaches on the *Drosophila* model, including tissue-targeted loss-of-function, to unravel some of the important cross-talks existing between organs for the control of growth at the global level. We develop these approaches to (i) unravel the molecular nature of tissue cross-talks involved in nutrient sensing and the control of insulin/IGF secretion; (ii) tackle the feed-back mechanisms linking the developmental clock to the growing state of tissues and organs.

1- Deciphering the cross-talk between the fat body and the brain for the control of growth

Our previous work highlighted the role of the fat body in orchestrating global growth in response to extrinsic factors like nutrition. Our data indicated that in response to favorable nutrients and in particular to amino acids, an unknown secretion signal emanating from fat cells transits through the hemolymph and instructs the brain to release the insulin-like peptides. The nature of this secretion factor is not known yet. We aim at characterizing the cross-talk between fat cells and the brain insulin-producing cells. For this purpose, we have carried out RNAi- based screens both in brain insulin-producing cells and in the fat body.

2- Identifying the feed-back mechanisms linking tissue growth with developmental timing

An important aspect of final size determination is the coordination of growth arrest among organs and its coupling with the program of development. We have recently identified Dilp8 in a screen for factors expressed in imaginal discs under perturbed growth. Dilp8 is able to suppress Ecdysone production and delay the end of growth. We are currently pursuing the analysis of Dilp8 function in coordinating growth and developmental programs. For this, we aim at identifying the receptor for Dilp8 and its target tissues, as well as the regulatory inputs on Dilp8 expression during normal development.

We also pursue the functional analysis of other candidate genes identified in the initial screen. One of them encodes a membrane-associated protein genetically positioned upstream of JNK signaling. Silencing this gene suppresses disc neoplastic growth, making it a strong candidate for a gene coupling epithelial integrity with JNK activation and overgrowth. We are currently investigating the function of this candidate, focusing on its role as a membrane sensor required for the activation of JNK signaling upon perturbation of epithelial polarity.

3- Hormonal coordination of developmental transitions

Previous work in insects has demonstrated a role for the PTTH hormone in the activation of ecdysteroid biosynthesis at the end of larval development. Therefore, it appears that this hormone serves an important timer function for a major developmental transition, marking the completion of larval growth, entry into maturation, metamorphosis and transition to adulthood. We investigate the control of PTTH production as a mean to understand the control of larval growth arrest. We focus our interest on the regulation of PTTH and ecdysone production by other signals than imaginal disc growth progression (cf our Dilp8 work). For this, we are carrying out RNAi-based screens for genes involved in the function of PTTH-producing neurons.

In the course of this work we have discovered that PTTH also controls larval light preference. We therefore propose that by acting on separate target organs, a single hormone like PTTH coordinates light preference and the time of pupariation. This work was carried out through collaboration with the group of Michael O'Connor (Minneapolis).

4- Modeling the homeostatic control of feeding behavior in flies.

We are interested in identifying the molecular and neuro-anatomical characteristics of the pathways controlling feeding behavior in the *Drosophila* larva. Earlier experiments have demonstrated that most animals rapidly evaluate the lack of essential amino acids (EAAs) in the food and present an aversion towards the imbalanced diet. The complexity of the vertebrate brain represents a considerable barrier to understanding the molecular mechanisms of such behavior and as a possible alternative we carry this analysis in the *Drosophila* brain.

We found that *Drosophila* larvae develop a rapid aversion toward EAAD and identified a molecular amino acid sensing mechanism taking place in the brain dopaminergic population. We continue investigating the role of the dopaminergic neuron population in the control of feeding during larval stages. Our current studies also aim at understanding the function of another important metabolic pathway, the insulin/IGF signaling pathway, in the control of feeding.