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Drosophila growth and development
Keeping things in proportion

Ditte S. Andersen,* Julien Colombani and Pierre Léopold

Institute of Biology Valrose; University of Nice-Sophia Antipolis; CNRS/INSERM UMR7277/1091; Nice, France

How is the growth of different body parts coordinated and scaled with the overall body size to give rise to adults of correct proportions? It is well established that different organs follow autonomous growth programs and therefore grow at different speeds and during distinct stages of development.[1] It is therefore likely that mechanisms operate to ensure that each organ has reached an appropriate size before proceeding through developmental transitions. If not, organs would be forced to terminate growth and differentiate prematurely, giving rise to disproportionate adults. How organ growth is monitored at the organismal level and how it is coupled with developmental transitions is not well understood.

In flies, a number of observations have been made regarding the coupling of organ growth and developmental transitions. The imaginal tissues (also called discs) of the larva are the equivalent of vertebrate limb buds and are the precursors of most of the visible organs in the adult fly. Perturbation of disc growth during early larval development delays larva-to-pupa transition.[2,3] This allows perturbed tissues to complete their growth programs and synchronise with other larval tissues before the steroid-induced transition to the pupal stage. Interestingly, larvae with little or no disc structures pupariate with normal timing.[4] In other words, the signal released from growing discs is an inhibitory signal that prevents pupariation until discs have completed their growth programs.

Recently, our group and the group of Maria Dominguez independently identified a novel hormone of the insulin family that could play an important role in coupling organ growth and animal maturation.[5,6]

To identify signals that couple organ growth with developmental transitions, we used a large-scale genetic approach. We designed two conditions where perturbation of disc growth induced robust delays in pupariation. These conditions were used sequentially to screen a collection of 11,000 transgenic RNAi lines, each of which reduced the expression of one specific gene, for the ability to rescue the delay in pupariation. Only one line efficiently rescued the delay in both of our conditions. This RNAi line targets the expression of a previously uncharacterized gene *CG14059*, encoding a small peptide of about 150 amino acids. Due to the presence of a conserved code of cysteines found in many insulin-like peptides, the gene was named *Drosophila insulin-like peptide 8 (dilp8)*. *dilp8* expression is highly upregulated in both of our test conditions, as well as in other conditions where perturbation of disc growth is associated with a delay in larva-to-pupa transition. These include regenerating discs, transdetermining discs[7] and discs carrying tumors. Indeed, *dilp8* was simultaneously identified by transcriptome analysis performed by Garelli et al. as a gene which is highly expressed in various eye disc tumors in Drosophila.[6]

In all these conditions, morphogens are re-expressed in patterns reminiscent of earlier developmental stages, suggesting that *dilp8* expression levels might be inversely related with disc maturity. Indeed, *dilp8* expression levels decrease during development, reaching its lowest levels towards the end of the third and last larval instar. Moreover, elevating *dilp8* expression levels specifically in the discs is sufficient to induce a robust developmental delay. In short, data from our and M. Dominguez's group are consistent with the notion that Dilp8 is secreted from discs with perturbed growth programs and acts remotely on the central brain complex to inhibit production of the molting steroid ecdysone.[5,6] Through this process, Dilp8 secreted from tissues with altered growth status can delay the hormonal events preceding pupariation, thus allowing tissues to synchronize their growth programs.

What could be the function of Dilp8 during "normal" development? Interestingly, Garelli et al. presents data showing that *dilp8* mutant animals exhibit considerable variation in final size and imperfect bilateral symmetry.[6] This suggests a role for *dilp8* in synchronizing growth between different organs in healthy animals. How might this be achieved? Circulating Dilp8 could act directly or through the production of a humoral signal to synchronize growth rates of different tissues. We noticed that expressing *dilp8* specifically in the discs leads to a slight growth retardation of both the discs and the overall body.[5,6] Thus, secretion of Dilp8 from slower growing or damaged discs might negatively affect growth of other organs as a mean of synchronizing growth rates of different tissues. This result is in line with a recent report showing that perturbing growth in a subset of discs reduces the growth rate of other discs.[8] In this case, the reduced growth rate of unperturbed discs could be rescued by feeding larvae ecdysone, thereby preventing coupling of growth between larval tissues.[8] It is interesting to speculate that Dilp8 could synchronize growth of different tissues via its inhibitory effect on ecdysone production.

The identification of Dilp8 as a new insulin-like peptide raises the possibility

*Correspondence to: Ditte S. Andersen; Email: andersen@unice.fr
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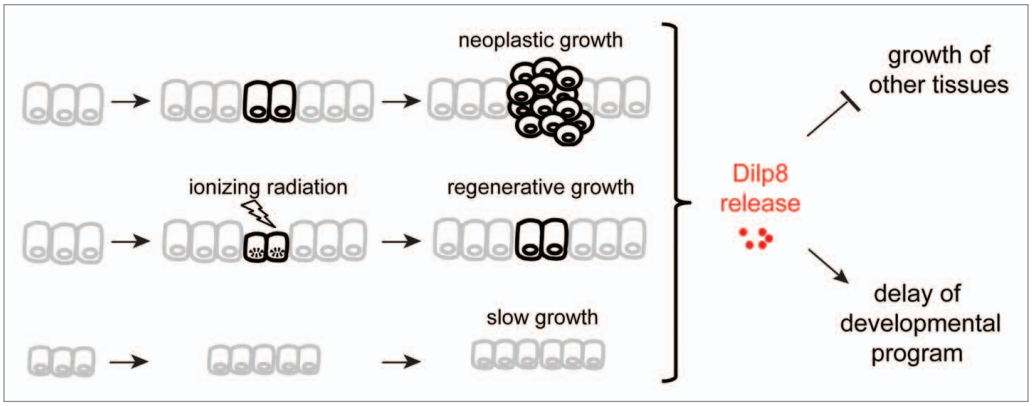

Figure 1. Coupling of organ growth and developmental transitions. The release of Dilp8 from discs with perturbed growth programs suppresses growth of other larval tissues and delays larva-to-pupa transition.

that functional homologs exist in vertebrates. Indeed, there is clinical evidence that tissue damage can lead to growth retardation in humans. Chronic inflammation, infections or tissue repair in children are often associated with growth retardation and delays in puberty.[9,10] Identifying the receptor for Dilp8 might shed light on whether the function of this molecule is conserved in humans.

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