

Année de publication : 2019

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Laura Boulan\*, Ditte Andersen, Julien Colombani, Emilie Boone, Pierre Léopold\*, (\*corr. authors)  
(2019 Apr 23)

**Inter-Organ Growth Coordination Is Mediated by the Xrp1-Dilp8 Axis in *Drosophila*.**

*Developmental cell* : DOI : [10.1016/j.devcel.2019.03.016](https://doi.org/10.1016/j.devcel.2019.03.016)

**Résumé**

How organs scale with other body parts is not mechanistically understood. We have addressed this question using the *Drosophila* imaginal disc model. When the growth of one disc domain is perturbed, other parts of the disc and other discs slow down their growth, maintaining proper inter-disc and intra-disc proportions. We show here that the relaxin-like Dilp8 is required for this inter-organ coordination. Our work also reveals that the stress-response transcription factor Xrp1 plays a key role upstream of dilp8 in linking organ growth status with the systemic growth response. In addition, we show that the small ribosomal subunit protein RpS12 is required to trigger Xrp1-dependent non-autonomous response. Our work demonstrates that RpS12, Xrp1, and Dilp8 form an independent regulatory module that ensures intra- and inter-organ growth coordination during development.

Derya Deveci, Francisco A Martin, Pierre Leopold\*, Nuria M Romero\*, (\*Corr. author) (2019 Feb 26)

**AstA Signaling Functions as an Evolutionary Conserved Mechanism Timing Juvenile to Adult Transition.**

*Current biology* : CB : 813-822.e4 : DOI : [10.1016/j.cub.2019.01.053](https://doi.org/10.1016/j.cub.2019.01.053)

**Résumé**

The onset of sexual maturation is the result of a hormonal cascade peaking with the production of steroid hormones. In animals undergoing a program of determinate growth, sexual maturation also coincides with the attainment of adult size. The exact signals that time the onset of maturation and the mechanisms coupling growth and maturation remain elusive. Here, we show that the *Drosophila* neuropeptide AstA and its receptor AstAR1 act as a brain trigger for maturation and juvenile growth. We first identified AstAR1 in an RNAi-based genetic screen as a key regulator of sexual maturation. Its specific knockdown in prothoracicotropic hormone (PTTH)-producing neurons delays the onset of maturation by impairing PTTH secretion. In addition to its role in PTTH neurons, AstAR1 is required in the brain insulin-producing cells (IPCs) to promote insulin secretion and systemic growth. AstAR1 function is mediated by the AstA neuropeptide that is expressed in two bilateral neurons contacting the PTTH neurons and the IPCs. Silencing brain AstA expression delays the onset of maturation, therefore extending the growth period. However, no pupal overgrowth is observed, indicating that, in these conditions, the growth-promoting function of AstAR1 is also impaired. These data suggest that AstA/AstAR1 acts to coordinate juvenile growth with maturation. Interesting, AstA/AstAR1 is homologous to KISS/GPR54, a ligand-receptor signal

required for human puberty, suggesting that an evolutionary conserved neural circuitry controls the onset of maturation.

#### Année de publication : 2018

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Eleonora Meschi, Pierre Léopold\*, Renald Delanoue, (\*Corr. author) (2018 Dec 10)

#### **An EGF-Responsive Neural Circuit Couples Insulin Secretion with Nutrition in *Drosophila*.**

*Developmental cell* : [DOI : 10.1016/j.devcel.2018.11.029](https://doi.org/10.1016/j.devcel.2018.11.029)

#### Résumé

Developing organisms use fine-tuning mechanisms to adjust body growth to ever-changing nutritional conditions. In *Drosophila*, the secretory activity of insulin-producing cells (IPCs) is central to couple systemic growth with amino acids availability. Here, we identify a subpopulation of inhibitory neurons contacting the IPCs (IPC-connecting neurons or ICNs) that play a key role in this coupling. We show that ICNs respond to growth-blocking peptides (GBPs), a family of fat-body-derived signals produced upon availability of dietary amino acids. We demonstrate that GBPs are atypical ligands for the fly EGF receptor (EGFR). Upon activation of EGFR by adipose GBPs, ICN-mediated inhibition of IPC function is relieved, allowing insulin secretion. Our study reveals an unexpected role for EGF-like metabolic hormones and EGFR signaling as critical modulators of neural activity, coupling insulin secretion to the nutritional status.

MaryJane Shimell, Xueyang Pan, Francisco A Martin, Arpan C Ghosh, Pierre Leopold, Michael B O'Connor, Nuria M Romero (2018 Feb 23)

#### **Prothoracicotropic hormone modulates environmental adaptive plasticity through the control of developmental timing.**

*Development (Cambridge, England)* : [DOI : dev159699](https://doi.org/10.1016/j.dev.2018.02.009)

#### Résumé

Adult size and fitness are controlled by a combination of genetics and environmental cues. In , growth is confined to the larval phase and final body size is impacted by the duration of this phase, which is under neuroendocrine control. The neuropeptide prothoracicotropic hormone (PTTH) has been proposed to play a central role in controlling the length of the larval phase through regulation of ecdysone production, a steroid hormone that initiates larval molting and metamorphosis. Here, we test this by examining the consequences of null mutations in the gene for development. Loss of causes several developmental defects, including a delay in developmental timing, increase in critical weight, loss of coordination between body and imaginal disc growth, and reduced adult survival in suboptimal environmental conditions such as nutritional deprivation or high population density. These defects are caused by a decrease in ecdysone production associated with altered transcription of ecdysone biosynthetic genes. Therefore, the PTTH signal contributes to coordination between

environmental cues and the developmental program to ensure individual fitness and survival.

#### Année de publication : 2016

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Renald Delanoue, Eleonora Meschi, Neha Agrawal, Alessandra Mauri, Yonit Tsatskis, Helen McNeill, Pierre Léopold (2016 Oct 7)

#### **Drosophila insulin release is triggered by adipose Stunted ligand to brain Methuselah receptor.**

*Science (New York, N.Y.)* : 1553-1556

#### Résumé

Animals adapt their growth rate and body size to available nutrients by a general modulation of insulin-insulin-like growth factor signaling. In *Drosophila*, dietary amino acids promote the release in the hemolymph of brain insulin-like peptides (Dilps), which in turn activate systemic organ growth. Dilp secretion by insulin-producing cells involves a relay through unknown cytokines produced by fat cells. Here, we identify Methuselah (Mth) as a secretin-incretin receptor subfamily member required in the insulin-producing cells for proper nutrient coupling. We further show, using genetic and ex vivo organ culture experiments, that the Mth ligand Stunted (Sun) is a circulating insulinotropic peptide produced by fat cells. Therefore, Sun and Mth define a new cross-organ circuitry that modulates physiological insulin levels in response to nutrients.

Neha Agrawal, Renald Delanoue, Alessandra Mauri, Davide Basco, Matthieu Pasco, Bernard Thorens, Pierre Léopold (2016 Apr 15)

#### **The Drosophila TNF Eiger Is an Adipokine that Acts on Insulin-Producing Cells to Mediate Nutrient Response.**

*Cell metabolism* : 675-84 : [DOI : 10.1016/j.cmet.2016.03.003](https://doi.org/10.1016/j.cmet.2016.03.003)

#### Résumé

Adaptation of organisms to ever-changing nutritional environments relies on sensor tissues and systemic signals. Identification of these signals would help understand the physiological crosstalk between organs contributing to growth and metabolic homeostasis. Here we show that Eiger, the *Drosophila* TNF- $\alpha$ , is a metabolic hormone that mediates nutrient response by remotely acting on insulin-producing cells (IPCs). In the condition of nutrient shortage, a metalloprotease of the TNF- $\alpha$  converting enzyme (TACE) family is active in fat body (adipose-like) cells, allowing the cleavage and release of adipose Eiger in the hemolymph. In the brain IPCs, Eiger activates its receptor Grindelwald, leading to JNK-dependent inhibition of insulin production. Therefore, we have identified a humoral connexion between the fat body and the brain insulin-producing cells relying on TNF- $\alpha$  that mediates adaptive response to nutrient deprivation.

Année de publication : 2015

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Julien Colombani, Ditte S Andersen, Laura Boulan, Emilie Boone, Nuria Romero, Virginie Virolle, Michael Texada, Pierre Léopold (2015 Oct 7)

**Drosophila Lgr3 Couples Organ Growth with Maturation and Ensures Developmental Stability.**

*Current biology* : CB : 2723-9 : [DOI : 10.1016/j.cub.2015.09.020](https://doi.org/10.1016/j.cub.2015.09.020)

**Résumé**

Early transplantation and grafting experiments suggest that body organs follow autonomous growth programs [1-3], therefore pointing to a need for coordination mechanisms to produce fit individuals with proper proportions. We recently identified *Drosophila* insulin-like peptide 8 (Dilp8) as a relaxin and insulin-like molecule secreted from growing tissues that plays a central role in coordinating growth between organs and coupling organ growth with animal maturation [4, 5]. Deciphering the function of Dilp8 in growth coordination relies on the identification of the receptor and tissues relaying Dilp8 signaling. We show here that the orphan receptor leucine-rich repeat-containing G protein-coupled receptor 3 (Lgr3), a member of the highly conserved family of relaxin family peptide receptors (RXFPs), mediates the checkpoint function of Dilp8 for entry into maturation. We functionally identify two Lgr3-positive neurons in each brain lobe that are required to induce a developmental delay upon overexpression of Dilp8. These neurons are located in the pars intercerebralis, an important neuroendocrine area in the brain, and make physical contacts with the PTTH neurons that ultimately control the production and release of the molting steroid ecdysone. Reducing Lgr3 levels in these neurons results in adult flies exhibiting increased fluctuating bilateral asymmetry, therefore recapitulating the phenotype of dilp8 mutants. Our work reveals a novel Dilp8/Lgr3 neuronal circuitry involved in a feedback mechanism that ensures coordination between organ growth and developmental transitions and prevents developmental variability.

Ditte S Andersen, Julien Colombani, Valentina Palmerini, Krittalak Chakrabandhu, Emilie Boone, Michael Röthlisberger, Janine Toggweiler, Konrad Basler, Marina Mapelli, Anne-Odile Hueber, Pierre Léopold (2015 Apr 16)

**The Drosophila TNF receptor Grindelwald couples loss of cell polarity and neoplastic growth.**

*Nature* : 482-6 : [DOI : 10.1038/nature14298](https://doi.org/10.1038/nature14298)

**Résumé**

Disruption of epithelial polarity is a key event in the acquisition of neoplastic growth. JNK signalling is known to play an important part in driving the malignant progression of many epithelial tumours, although the link between loss of polarity and JNK signalling remains elusive. In a *Drosophila* genome-wide genetic screen designed to identify molecules implicated in neoplastic growth, we identified *grindelwald* (*grnd*), a gene encoding a transmembrane protein with homology to members of the tumour necrosis factor receptor

(TNFR) superfamily. Here we show that Grnd mediates the pro-apoptotic functions of Eiger (Egr), the unique *Drosophila* TNF, and that overexpression of an active form of Grnd lacking the extracellular domain is sufficient to activate JNK signalling in vivo. Grnd also promotes the invasiveness of Ras(V12)/scrib(-/-) tumours through Egr-dependent Matrix metalloprotease-1 (Mmp1) expression. Grnd localizes to the subapical membrane domain with the cell polarity determinant Crumbs (Crb) and couples Crb-induced loss of polarity with JNK activation and neoplastic growth through physical interaction with Veli (also known as Lin-7). Therefore, Grnd represents the first example of a TNFR that integrates signals from both Egr and apical polarity determinants to induce JNK-dependent cell death or tumour growth.

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**Année de publication : 2014**

Marianne Bjordal, Nathalie Arquier, Julie Kniazeff, Jean Philippe Pin, Pierre Léopold (2014 Feb 4)

**Sensing of amino acids in a dopaminergic circuitry promotes rejection of an incomplete diet in *Drosophila*.**

*Cell* : 510-21 : [DOI : 10.1016/j.cell.2013.12.024](https://doi.org/10.1016/j.cell.2013.12.024)

**Résumé**

The brain is the central organizer of food intake, matching the quality and quantity of the food sources with organismal needs. To ensure appropriate amino acid balance, many species reject a diet lacking one or several essential amino acids (EAAs) and seek out a better food source. Here, we show that, in *Drosophila* larvae, this behavior relies on innate sensing of amino acids in dopaminergic (DA) neurons of the brain. We demonstrate that the amino acid sensor GCN2 acts upstream of GABA signaling in DA neurons to promote avoidance of the EAA-deficient diet. Using real-time calcium imaging in larval brains, we show that amino acid imbalance induces a rapid and reversible activation of three DA neurons that are necessary and sufficient for food rejection. Taken together, these data identify a central amino-acid-sensing mechanism operating in specific DA neurons and controlling food intake.

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**Année de publication : 2013**

Naoki Yamanaka, Nuria M Romero, Francisco A Martin, Kim F Rewitz, Mu Sun, Michael B O'Connor, Pierre Léopold (2013 Sep 7)

**Neuroendocrine control of *Drosophila* larval light preference.**

*Science (New York, N.Y.)* : 1113-6 : [DOI : 10.1126/science.1241210](https://doi.org/10.1126/science.1241210)

**Résumé**

Animal development is coupled with innate behaviors that maximize chances of survival. Here, we show that the prothoracicotrophic hormone (PTTH), a neuropeptide that controls the developmental transition from juvenile stage to sexual maturation, also regulates light



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avoidance in *Drosophila melanogaster* larvae. PTTH, through its receptor Torso, acts on two light sensors—the Bolwig's organ and the peripheral class IV dendritic arborization neurons—to regulate light avoidance. We found that PTTH concomitantly promotes steroidogenesis and light avoidance at the end of larval stage, driving animals toward a darker environment to initiate the immobile maturation phase. Thus, PTTH controls the decisions of when and where animals undergo metamorphosis, optimizing conditions for adult development.