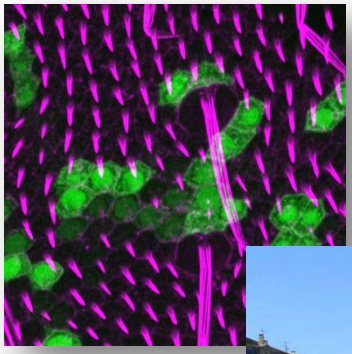
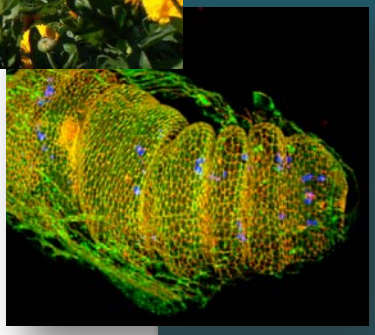
28th Annual French Drosophila Conference



Invited speakers:

Clemens Cabernard
Marc Dionne
Bénédicte Durand
Alex Gould
Yacine Graba
Mounia Lagha
Stéphane Noselli
Pauline Speder



Sète 2014

Relais Cap France LE LAZARET

27-30 Octobre

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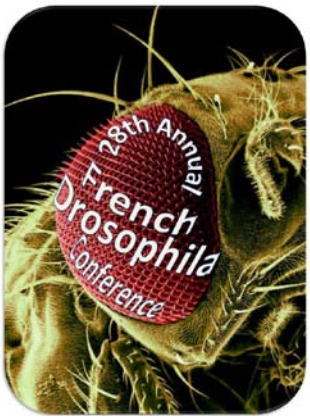
Organizing committee: Michèle CROZATIER, Jean-Louis FRENDO, Guillaume ISABEL, Serge PLAZA, Magali SUZANNE and Xiaobo WANG

Program

28th Annual French
Drosophila Conference

Sète - France
27-30 octobre 2014



MONDAY OCTOBER 27th

16h15-16h30: ***WELCOME***

A-Morphogenesis and organogenesis

CHAIR: Jean-Antoine LEPESANT and Stéphane NOSELLI

16h30-16h50: **C. BENASSAYAG,** Toulouse
The Drosophila Hox gene Deformed drives tissue boundary fold formation through regulation of sub cellular DE-Cadherin distribution.

16h50-17h10: **M. SUZANNE,** Toulouse
Apico-basal forces exerted by apoptotic cells drive epithelium folding.

17h10-17h30: **F. AGNES,** Paris XI
JAK/STAT signaling regulates anoïkis in the Drosophila follicular epithelium.

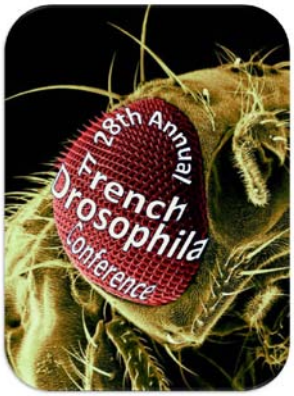
17h30-17h50: **A. COMBEDAZOU,** Toulouse
Two different modes of collective cell movement.

17h50-18h10: **X. QIN,** Toulouse
Controlling mechanism of basal actomyosin oscillation during Drosophila ovary development.

19h15: ***Dinner***

20h30-21h15: **PLENARY SESSION: Stéphane NOSELLI**
Left-Right asymmetry in Drosophila.

Bar



TUESDAY OCTOBER 28th

B- Cell cycle/ Cell growth/Cell Signaling

CHAIR: Clemens CABERNARD and Frédérique PERONNET

9h00-9h45: **PLENARY SESSION: Clemens CABERNARD**
Cellular and molecular mechanisms during asymmetric cell division.

9h45-10h05: **F. JANODY,** Lisboa
Cytoskeletal regulators couple F-actin dynamics to Yorkie-dependent organ growth.

10h05- 10h25: **E. BOONE,** Nice
The coupling of disc size sensing mechanism and Dilp8 expression.

10h25-11h00: ***Coffee***

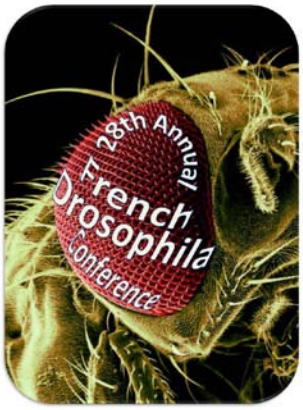
11h00-11h20: **S. ZAESSINGER,** Montpellier
Drosophila MAGI interacts with dRASSF8 to regulate E-Cadherin based Adherens Junctions in the developing eye.

11h20-11h40: **I. MORIN-POULARD ,** Toulouse
Characterization of the Drosophila hematopoietic niche: role of the Slit/Robo signaling pathway.

11h40-12h00: **F. NAPOLETANO,** Lyon
p53-dependent necrosis suppresses tumorigenesis in Drosophila.

12h00-12h15: **NIKON/ANDOR presentation**

12h30: ***Lunch***



C- Immunity, non-coding RNA, epigenetic, Models for human diseases

CHAIR: Marc DIONNE and Yacine GRABA

14h00 -14h20: **N. MALMANCHE,** Lille
Human Tau expression during Drosophila development strongly affects mitotic progression and chromosome segregation.

14h20-14h40: **A. ISSA,** Paris
Neuronal expression of mitochondrial uncoupling proteins increases oxidative stress resistance and protects against functional senescence in Drosophila.

14h40-15h00: **D. ANDERSEN,** Nice
The Drosophila TNF receptor Grindelwald couples loss of cell polarity with neoplastic growth.

15h00-15h45: **PLENARY SESSION: Marc DIONNE**
Immune-metabolic interactions in Drosophila.

15h45-16h15: ***coffee***

16h15-16h35: **C. SOCHA,** Strasbourg
Study of resilience and proteostasis during intestinal infections in Drosophila.

16h35-16h55: **C.E. INDELICATO,** Lyon
Mechanisms underlying Lactobacilli-mediated juvenile growth promotion: "learning on the fly".

16h55- 17h15: **J. DUFOURT,** Montpellier
Rôle de la voie des piARN dans la régulation des ARN messagers maternels.

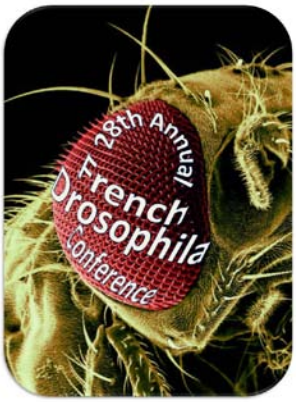
17h15-17h35: **P. MARIE;** Paris VI
"piRNA-mediated repression during Drosophila development".

17h35-17h55: **J. DERAZE,** Paris VII
Epigenetic control of ribosome biogenesis: deciphering the role of RPL12 in transcription.

19h15: ***Dinner***

20h30-21h15**: PLENARY SESSION: Yacine GRABA**
Insights into mechanisms and biology of Hox proteins.

21h15: ***Posters and drinks***



WEDNESDAY OCTOBER 29th

D- Morphogenesis and organogenesis

CHAIR: Mounia LAGHA and Alain VINCENT

9h00-9h45: **PLENARY SESSION: Mounia LAGHA**
Exploring the role of paused polymerase on transcriptional dynamics.

9h45-10h05: **D. SEYRES,** Marseille
Genome wide identification of cis-regulatory elements from (very) small cell population: Insights from the drosophila cardiac tube.

10h05- 10h25: **H. CHANUT-DELALANDE,** Toulouse
Pri peptides are mediators of ecdysone for the temporal control of development.

10h25-11h00: ***Coffee***

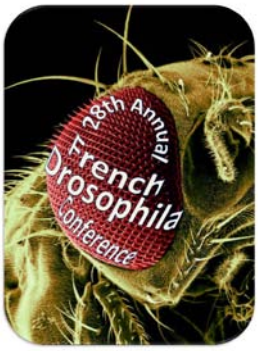
11h00-11h20: **L. BATAILLE,** Toulouse
An Org-1--Tup transcriptional cascade reveals the existence of different types of alary muscles connecting internal organs in Drosophila.

11h20-11h40: **N. GONZALEZ-MORALES**, Nice
The Atypical Cadherin Dachsous and Planar Cell Polarity control Left-Right Asymmetry in Drosophila.

11h40-12h00: **J. BOHERE,** Toulouse
The transcription factor Shavenbaby controls drosophila renal stem cells behaviour.

12h00-12h20: **A. DIB ,** Toulouse
Function and regulation mode of the pri gene during drosophila development.

12h30: ***Lunch***



E- Neurobiology / Stem cells

CHAIR: Pauline SPEDER and Bénédicte DURAND

14h00-14h45: **PLENARY SESSION: Pauline SPEDER**
Tell me what you eat: nutritional adaptation of neural stem cells.

14h45-15h05: **J.M. DURA,** Montpellier
Extrinsic DRL Guides DRL-2-expressing Drosophila Mushroom Body Axons by WNT5 Ligand presentation and Ectodomain Shedding.

15h05-15h25: **F. MARTIN,** Nice
Neuroendocrine Control of Drosophila Behavior.

15h25-16h00: ***coffee***

16h00-16h20: **M. GHO,** Paris VI
Precocious divisions promote self-renewal of sensory organ precursor cells.

16h20-16h40: **P. CATTENOZ,** Strasbourg
Decrypting the glia differentiation program.

16h40- 17h00: **C. FONS,** London
Molecular mechanisms of CNS sparing in Drosophila.

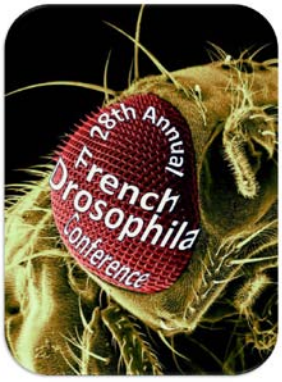
17h00-17h20: **M. ANDRIATSILAVO,** Paris
Split-ends : a new regulator of adult stem cells in Drosophila intestine.

17h20-18h05: **PLENARY SESSION: Bénédicte DURAND**
Cilia assembly in Drosophila: what can we learn?

18h05-18h45: **Business sessions**

19h15: ***Dinner***

DANCING



THURSDAY OCTOBER 30th

F- Physiology and Metabolism

CHAIR: Pierre LEOPOLD and Alex GOULD

9h30-10h15: **PLENARY SESSION: Alex GOULD**
Protecting the growing CNS from starvation and hypoxia.

10h15-10h35: **N. AGRAWAL,** Nice
The nutritional regulation of body size by the Drosophila TNF/JNK pathway.

10h35- 11h00: ***Coffee***

11h00-11h20: **M. TEFIT,** Lyon
Host-microbiota interactions: Effects of Lactobacillus plantarum on Drosophila adult physiology.

11h20-11h40: **A. GALLET,** Nice
A balance between JNK and Hippo signalling pathways maintains the cellular homeostasis of the intestine upon bacterial food poisoning.

12h00: ***Lunch***

Abstract plenary sessions

28th Annual French Drosophila Conference

Sète - France
27-30 octobre 2014

Left-Right asymmetry in Drosophila

Noselli S

Université de Nice Sophia-Antipolis
Nice - France

Breaking Left-Right (LR) symmetry in Bilateria is a major event in body plan organization. LR asymmetry is essential for positioning visceral organs, but is also essential for asymmetric morphogenesis and function of the heart and brain. Work using vertebrate models has revealed a number of original mechanisms underlying LR development, including the ‘nodal flow’, ‘ion flows’ and ‘cellular flow’. In contrast, the study of LR asymmetry in invertebrates has been less well developed. And although Drosophila represents a major model to study body patterning, LR asymmetry remained uncharacterized in this organism until recently. Here, I will present our current knowledge on genes, pathways and mechanisms underlying establishment of LR asymmetry in Drosophila and will discuss how these findings fit and contribute to our general understanding of LR asymmetry across phyla. In particular, I will describe specific organ LR organizers (genitalia, gut) and show how the Hox gene Abd-B and the conserved type ID myosin (MyoID) genes work together to control LR development in Drosophila and during evolution.

Cellular and molecular mechanisms during asymmetric cell division

Cabernard C

Biozentrum, University of Basel, Switzerland

Asymmetric cell division (ACD) generates cellular diversity. Stem and progenitor cells in particular utilize ACD to self-renew the stem/progenitor cell while also forming differentiated siblings. We are using Drosophila neural stem cells called neuroblasts, the precursors of the fly central nervous system, to study cellular, molecular and biophysical mechanisms of asymmetric cell division.

Recently, we have shown that the conserved centriolar component Bld10 (Cep135 in vertebrates) is required to establish centrosome asymmetry, a requirement for correct spindle orientation. In addition to Bld10, we isolated several new components involved in centrosome asymmetry, instrumental in obtaining a thorough molecular understanding of this process.

We are also studying Myosin dynamics during asymmetric cell division. Recently, I showed that Drosophila neuroblasts are utilizing a spindle-independent, polarity-dependent mechanism for cleavage furrow positioning. This pathway, consisting of the conserved polarity proteins Discs large 1 (Dlg) and Partner of Inscuteable (Pins; LGN/AGS3 in vertebrates) instructs the asymmetric localization of Myosin. Controlled cleavage furrow positioning is important for accurate cell fate determinant segregation and the correct partitioning of chromosomes. We have developed photoconversion assays to study the dynamics of Myosin during ACD and also identified a novel Myosin regulator, acting in the polarity-dependent cleavage furrow positioning pathway.

In my presentation, I will outline our recent progress on the establishment and maintenance of centrosome asymmetry. Furthermore, I will provide a progress report on Myosin dynamics and cleavage furrow positioning in Drosophila neuroblasts.

Immune-metabolic interactions in Drosophila

Dionne M

King’s college, London, UK

Immune responses and metabolic regulation are intimately linked in all animals. However, our understanding of the mechanistic underpinnings of this linkage is incomplete. I will present two different aspects of metabolic-immune interaction in Drosophila. In the first part of the talk, I will present our recent data showing that the transcription factor MEF2 is a critical switch between immune function and metabolic storage. Flies lacking MEF2 in the fat body exhibit dramatic reductions in storage of triglyceride and glycogen and are simultaneously severely immunocompromised; we have shown that these phenotypes reflect distinct transcriptional functions of MEF2, and that the loss of "metabolic" MEF2 contributes to the loss of anabolic enzyme expression in Gram-negative bacterial infection. In the second part of the talk, I will discuss the role of the Drosophila cytokine upd3 in regulation of phagocyte bactericidal activity and cellular lipid metabolism during mycobacterial infections. We have found that upd3 is produced by hemocytes in mycobacterium-infected flies, and that this signal is received by hemocytes and inhibits their ability to kill intracellular mycobacteria. We find that this effect may be partly mediated by effects on expression of Atg2; in this context, upd3-regulated Atg2 appears to be an important regulator of hemocyte lipid metabolism, and it is this effect on lipid metabolism that inhibits the ability of these cells to kill the invading bacteria.

Insights into mechanisms and biology of Hox proteins

Graba Y

IBDM, Marseille Luminy -France

Hox proteins are key actors of development, evolution and diseases. Our current view of how Hox proteins function is profoundly influenced by the early identification of PBC class proteins as general Hox cofactors. PBC proteins (referring to Drosophila Extradenticle and vertebrate PBX proteins) are HD containing proteins that physically associate through a unique interaction mode with Hox proteins to promote cooperative DNA binding, allowing for selective target gene recognition and specificity of action of Hox proteins. We have investigated Hox protein function within the confine of specificity conferred by interaction with PBC proteins, but also by exploring generic rather than specific Hox functions. Results suggest novel modes of Hox/PBC complex assembly and identify unusual functions in mediating temporal and environmental cues rather than spatial cues.

Exploring the role of paused polymerase on transcriptional dynamics

Ferraro T[1], Esposito E[2], Mancini L[2], Sam Ng[2], Dostatni N[1], Levine M[2], Lagha M[2,3]

1: Institut Curie-CNRS, UMR218/UMR168/UMR8549/UMR8550, Paris, France.
2: UC Berkeley, Molecular and Cellular Biology Department, GDD, UC Berkeley, USA.
3: CNRS-IGMM, UMR5535, Montpellier, France. http://laghalab.com

Paused RNA polymerase (Pol II) is a pervasive feature of Drosophila embryos and mammalian stem cells, but its role in development is uncertain.

To determine whether synchronous patterns of gene activation are significant in development, we manipulated the timing of snail expression, which controls the coordinated invagination of ~1,000 mesoderm cells during gastrulation. Replacement of the strongly paused snail promoter with moderately paused or nonpaused promoters causes stochastic activation of snail expression and increased variability of mesoderm invagination. We conclude that paused Pol II and transcriptional synchrony are essential for coordinating cell behavior during morphogenesis.

Here, we use the newly available technique of live imaging of transcription (MS2-MCP system) to monitor activation dynamics from various enhancer/promoter synthetic constructs.

We quantify the time to synchrony for various promoter sequences and characterize the role of promoter elements on transcription dynamics.

Interestingly, using a sensitized snail enhancer, we reveal the existence of a transcription ''memory'' whereby the transcriptional activity of a given nuclei is inherited through mitosis.

Tell me what you eat: nutritional adaptation of neural stem cells.

Speder P

University of Cambridge, UK

Throughout life, an organism has to face changes in food availability, and must tailor its response to either lack or excess of some or all nutrients. The brain itself reacts to such changes, which impacts on its development or on its cognitive functions during adulthood. Neural stem cells are multipotent progenitors that self-renew and produce neuronal and glial progeny. They are able to switch from quiescence to division, or alter their differentiation program in response to metabolic changes. How NSCs are able to sense and interpret these changes is a challenging and outstanding question.

Drosophila NSCs enter a quiescent phase at the end of embryogenesis, from which they are later able to awake upon amino-acid feeding. This nutritional intake is sensed by the fat body, which sends a yet-to-be-identified factor that in turn triggers the production and secretion of insulin-like peptides (dIlps) from surface glial cells. dIlps bind to the insulin receptor on the surface of NSCs and activate the canonical PI3K/Akt pathway, triggering both growth and mitotic entry of NSCs. Recent findings have identified the blood-brain barrier as a sensing interface between nutrition and NSC reactivation. A combination of gap junction communication and calcium signalling enables the blood-brain barrier to convert the nutritional signal into efficient dIlp signalling. Integrating these latest data in the current model will allow us to draw a paradigm of how NSCs adapt to nutritional changes.

Cilia assembly in drosophila: what can we learn?

Durand B

Centre de génétique et de physiologie moléculaire et cellulaire
UMR 5534
Lyon - France

Cilia are highly conserved organelles found across species from protozoa to mammals. Cilia play major functions in cell physiology and tissue homeostasis. Ciliary dysfunctions lead to a variety of human diseases called ciliopathies. In Drosophila, cilia are found on the sensory neurons in the peripheral nervous system and on the sperm cells. Sensory cilia can be motile or immotile and require a specific molecular transport machinery, the intraflagellar transport (IFT), for their assembly. Sperm flagella are motile and do not require IFT. This makes Drosophila a particularly suited model to distinguish the respective function of genes in IFT associated mechanisms, in ciliary structure or in cilia motility.

We have shown that the RFX transcription factor is a key regulator of ciliogenesis in Drosophila and that this function is conserved for its mouse ortholog RFX3. I will discuss how our work on the RFX transcriptional network led to the identification of several novel genes required for ciliogenesis and how our functional studies of these genes in Drosophila can bring novel understandings on cilia assembly.

Protecting the growing CNS from starvation and hypoxia

Bailey AP[1], Koster G[2], Guillermier C[3], Lechene C[3], Postle AD[2], Gould AP[1]*

1: Division of Physiology & Metabolism, Medical Research Council, National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA, UK
2: Academic Unit of Clinical & Experimental Sciences, Faculty of Medicine, Southampton General Hospital, Southampton SO16 6YD, UK
3: National Resource for Imaging Mass Spectroscopy, Harvard Medical School and Brigham and Women's Hospital, Cambridge, Massachusetts 02139, USA

*: agould@nimr.mrc.ac.uk

Developing animals can withstand a variety of different environmental stresses but, in many cases, the underlying mechanisms are not yet clear. Research in the lab has identified protective mechanisms that function to spare the proliferation of neural stem cells (neuroblasts) in the developing CNS of Drosophila. For example, during the juvenile phase of Drosophila development, we found that neuroblasts are able to grow and proliferate at near normal levels even in the complete absence of dietary nutrients. Clonal analysis demonstrated that this cell-type specific mode of growth, known as brain sparing, requires Anaplastic Lymphoma Kinase but surprisingly not the Insulin/IGF receptor or Target of Rapamycin (TOR). More recent work has shown that the proliferation of neuroblasts, unlike that of most other cell types, is also protected against hypoxia. Genetics, imaging mass spectrometry and metabolomics approaches show that the underlying protective mechanism requires specialized lipid metabolism in the local microenvironment (the stem cell niche) rather than in the neuroblasts themselves. These studies begin to explain the remarkable resistance of the developing brain to environmental stresses and they also highlight metabolic parallels between fly neuroblasts and some mammalian tumors.

Abstract short talks

28th Annual French Drosophila Conference

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The Drosophila Hox gene Deformed drives tissue boundary fold formation through regulation of sub cellular DE-Cadherin distribution.

Benassayag Corinne [1], Tiberghien Marie-Anais, Lebreton Gaelle, Cribbs David, Suzanne Magali

1 : Université Toulouse III, CNRS, UMR 5088 (LBCMCP)
CNRS : UMR5088Université Toulouse III - Paul Sabatier - IUT de Tarbes
université Paul Sabatier, bat 4R3, 118 route de Narbonne, 31062 Toulouse Cedex
http://www-lbcmcp.ups-tlse.fr/Nouveau_site/modeles/LBCMCP-Accueil.htm

Recent work indicates that Hox genes are involved in forming tissue boundaries, but, little is known about the cellular mechanisms involved. In Drosophila melanogaster, the eye-antennal (E-A) imaginal disc gives rise to several adult organs originating from territories defined in the disc: eyes, antennae and Maxillary palps (Mx). The Hox gene Deformed (Dfd/ Hoxb4-d4) is required for adult Mx palp organogenesis and participates in defining the Mx field. Here we report that, differential Dfd expression between Mx field and Peripodial Epithelium (PE) establishes a fold at the Mx-PE boundary forming a barrier of segregation essential for Mx morphogenesis. We show that specific basal accumulation of the adhesion molecule in the Mx cells, DE-Cadherin (DE-Cad) generates a basal constriction required for Mx-PE boundary fold formation and depends on Dfd expression level. Indeed, by clonal analysis we show that strong Dfd expression level is sufficient to induce cell-autonomous basal redistribution of DE-Cad leading to fold formation with neighboring cells weakly expressing Dfd. Dfd differential expression observed between Mx field and PE is thus sufficient to induce fold formation through basal redistribution of DE-cad since basal DE-cad is strictly required for Dfd dependent folding. This work reveals that a Hox gene coordinates tissue remodelling and boundary fold formation critical for organogenesis through regulation of DE-Cad sub-cellular distribution.

Apico-basal forces exerted by apoptotic cells drive epithelium folding

Suzanne Magali [1]

1 : Laboratoire de Biologie Cellulaire et Moleculaire du Control de la Proliferation (LBCMCP)
Université Paul Sabatier-Toulouse III - UPSCNRS : UMR5088
Université Paul Sabatier, Bat IVR3 B1 118 route de Narbonne
http://www-lbcmcp.ups-tlse.fr/Nouveau_site/modeles/LBCMCP-Accueil.htm

Epithelium folding is a basic morphogenetic event essential to transform simple 2D epithelial sheets into 3D structures, in both vertebrates and invertebrates. Folding has been shown to rely either on apical junction basal shifting or apical constriction that can be associated with baso-lateral shortening. The resulting cell shape changes depend on Myosin II redistribution which could be driven by mechanical signals. Yet, the initial cellular mechanisms that trigger and coordinate cell remodelling remain largely unknown.
Here, we unravel the active role of apoptotic cells in initiating morphogenesis, thus revealing a novel mechanism of epithelium folding. We show that, in a live developing tissue, apoptotic cells exert a transient pulling force upon the apical surface of the epithelium through an unexpected maintenance of their adherens junctions which link up with an highly dynamic apico-basal Myosin II cable, specific to apoptotic cells. The apoptotic cells then induce a non-autonomous increase in tissue tension and apical constriction in the surrounding tissue, eventually resulting in epithelium folding. By integrating data from a theoretical biophysical 3D model and in vivo ectopic apoptosis experiments, our data further reveal the importance of the cumulative effect of apoptotic cells in converting a naive, flat epithelium into a folded one.
Together, our results identify an apoptotic Myosin II dependent signal as the initial signal responsible for cortical Myosin II apical stabilisation, leading to cell reorganisation and tissue folding. This work further reveals that, far from being passively eliminated as generally assumed (e.g. during digit individualisation), apoptotic cells actively influence their surroundings and trigger tissue remodelling through regulation of tissue tension.

JAK/STAT signaling regulates anoïkis in the Drosophila follicular epithelium

Torres Alba [1], Pret Anne-Marie [,2*], Agnès François [,3*]

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Université Paris XI - Paris SudCNRS : UPR3404
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* : Corresponding author

Although much has been learned about the basic apoptotic machinery, far less is known about its activation in the context of the removal of cells from a tissue. Furthermore, the mechanistic basis for the dramatic cell shape and adhesion modifications occurring at the single cell level during exclusion and the role of neighboring cells in the physical disengagement of cells committed to death, in terms of mechanics and signaling are also weakly documented.
Polar cells (PCs), a specialized subset of epithelial cells located at the poles of Drosophila follicles, are produced in small excess (1-4 cells) and die one after another such that exactly 2 PCs survive. Here, we show that supernumerary PCs undergo a peculiar sequence of cell remodeling events before the apoptotic machinery is activated. Each PC destined to die is progressively enveloped becoming fully embedded between the 2 surviving PCs. During envelopment, apical volume specifically decreases and contacts with adjacent follicle cells (FCs) are progressively lost, while E-Cadherin-mediated adhesion is strengthened between PCs. Then, the E-Cadherin/Par3 enriched apically-constricted domain sinks slightly basally. Next, the cell enters apoptosis and E-Cadherin-mediated adhesion decreases in a caspase-dependent manner. Live imaging shows that PC envelopment takes hours, but that within minutes after full apical and basal envelopment, the cell fragments into apoptotic corpses, which are concomitantly expulsed laterally and then phagocytized by neighboring FCs. These results suggest that PC elimination resembles anoïkis in that it involves a 3-step process: 1) complex remodeling events, 2) apoptosis, 3) phagocytosis. We also show that JAK/STAT activity in the surrounding FCs is necessary for PC remodeling and subsequent apoptosis, as well as for the proper distribution of an active myosin meshwork in FCs. We are currently testing a model in which JAK/STAT-dependent force/tension generation in FCs would be implicated in apoptotic elimination of supernumerary PCs.

Two different modes of collective cell movement

Combedazou Anne [1*], Gay Guillaume [,2], Cadamuro Valérie [1], Ramel Damien [1], Wang Xiaobo [1]

1 : Laboratoire de biologie cellulaire et moléculaire du contrôle de la prolifération (LBCMCP)
CNRS : UMR5088
2 : DamCB
DamCB
* : Corresponding author

Collective cell migration is a central process during embryo morphogenesis, wound repair and cancer invasion. This coordinated migratory behavior is mainly referred as a polarized cell movement, in which chemoattractant gradients control the choice of leader cells from followers. However, this concept of leadership during collective chemotaxis is contradictory to a rotation or tumbling movement reported in collective border cell migration during Drosophila ovary development. This rotational phase is poorly understood, notably because of a lack of tools to precisely quantify it and discriminate it from the polarized non-rotational phase in a 3D context. Consequently, the controlling mechanism and biological function of collective rotation are still completely unknown.
To address these questions, we used ex vivo culture and time-lapse live cell imaging to monitor and measure different movements of border cell cluster, in WT and various genetic background. We demonstrated that the cross-talk between the ROCK ? Non-muscle MyosinII (NMII) signaling and the polarized activity of small GTPase Rac governs the transition between polarized non-rotational and rotational modes of collective migration. We found that the occurrence of rotation is mainly dependent on the activities of ROCK and NMII in collective cluster. Oppositely, the polarized Rac activity protrusion is correlated with the polarized non-rotational behavior. In order to confirm the switch control of collective polarized non-rotation vs. rotation by this signaling cross-talk, we used the genetic manipulation and an optogenetic tool called photoactivatable-Rac to change the ROCK/NMII activity and the Rac polarity respectively. We demonstrated that the ROCK/NMII activity and the Rac polarity antagonize each other. Our further work indicated that the ROCK/NMII signaling negatively affects the Rac activity and protrusion formation locally, which thus leads to a global control of the polarized distribution of both Rac activity and protrusion within border cell cluster.

Controlling mechanism of basal actomyosin oscillation during Drosophila ovary development

Qin Xiang [1], Klapholz Benjamin [,2], Hahn Klaus [,3], Wang Xiaobo [1*]

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2 : Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, United Kingdom
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In epithelia, individual cell is split into apical and basolateral regions. Recently, periodic contraction of actomyosin network has been described to occur in apical domain of different epithelial in order to achieve various morphological processes; such as apical constriction and germ band intercalation. Previously we demonstrated a pulsatile actomyosin contraction in basal surface to induce tissue elongation during Drosophila ovary development. However, the molecular mechanism controlling this oscillation remains unclear.
Our previous work implicated the potential role of E-cadherin or Integrin in the control of basal actomyosin oscillation. Following this study, firstly we demonstrated that the intensity of ?-Integrin or Talin, but not E-cadherin, was positively correlated to the level of basal non-muscle myosin II (myosin). Genetic manipulation or collagenase treatment both greatly reduced the level and distribution of basal actomyosin contraction, thus prevented tissue elongation. These indicate that Integrin/Talin complex might function as the direct upstream signal control. We hypothesized that the physical interaction of ?-Integrin/Talin could stimulate the downstream signal to mediate basal actomyosin oscillation. Within this downstream RhoGEF2-Rho1-ROCK signaling pathway, we surprisingly found that RhoGEF2 and Rho1 were mainly distributed near the plasma membrane, while ROCK were highly located in the cytosol cortex. During a periodic contraction cycle, ROCK shuttled between plasma membrane and cytosol, which was concurrent with actomyosin contraction flow; it suggests that this shuttle movement of ROCK might control the activation and inhibition status. Inhibition of either F-actin or myosin shut down only one signaling oscillation while inhibition of Rho1 blocked both, indicating that upstream signaling oscillation, even without mechanic force, might play the key role in basal actomyosin oscillation. Finally, we applied an optogenetic tool called LovTrap to simulate actomyosin oscillation in mammalian MDCK cells. Altogether, our study demonstrated the underlying mechanism of basal actomyosin oscillation in epithelial cells during Drosophila ovary development.

Cytoskeletal regulators couple F-actin dynamics to Yorkie-dependent organ growth

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Coordinated multicellular growth during development is achieved by the sensing of spatial and nutritional boundaries. The conserved Hippo (Hpo) signalling pathway has been proposed to restrict tissue growth by perceiving mechanical constraints through actin cytoskeleton networks. The actin-associated LIM-proteins Zyxin (Zyx) has been linked to the control of tissue growth via regulation of Hpo signalling, but the study of Zyx has been hampered by a lack of genetic tools. We generated a zyx mutant in Drosophila using TALEN endonucleases, and used this to show that Zyx antagonises the FERM-domain protein Expanded (Ex) to control tissue growth and eye differentiation. Also, Zyx membrane targeting promotes the interaction between the transcriptional co-activator Yorkie (Yki) and the transcription factor Scalloped (Sd), leading to activation of Yki target gene expression and promoting tissue growth. Finally, we show that Zyx's growth-promoting function is regulated by its interaction with the actin-associated protein Enabled via a conserved LPPPP-motif, and is antagonized by Capping Proteins. Our results show that Zyx is a functional antagonist of Ex in growth control, and establish a link between actin filament polymerisation and Yki activity.

The coupling of disc size sensing mechanism and Dilp8 expression

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Growth of different body parts needs to be coordinated and scaled with the overall body size to give rise to adults of correct proportions. Since different organs follow autonomous growth programs and therefore grow at different speeds and during distinct stages of development, mechanisms must operate to ensure that each organ has reached an appropriate size before proceeding through developmental transitions. We recently identified Drosophila insulin-like peptide 8 in a genetic screen for molecules coupling organ growth with developmental transitions. Dilp8 is secreted from abnormally growing tissues and acts on the brain complex to delay pupariation. Interestingly, dilp8 expression levels drops at the end of larval development suggesting a direct coupling between autonomous organ growth programs and dilp8 expression. Identifying signals that regulate dilp8 expression during normal development is therefore likely to provide a better understanding of organ size assessment mechanisms.
The Hippo tumour suppressor pathway plays a major function in restricting organ growth by promoting cell cycle exit and apoptosis. Hippo signalling is highly responsive to the mechanical forces operating in growing organs making it an ideal candidate for assessing organ size. Activation of the Hippo pathway restricts nuclear translocation of the transcriptional co-activator Yorkie, which together with its DNA-binding partner Scalloped, regulates downstream growth-promoting target genes. We show here that Yorkie is necessary and sufficient for inducing dilp8 expression and the associated delay in pupariation. Using a molecular biology approach, we demonstrate that Scalloped/Yorkie binds directly to three Hippo Responsive Elements (HREs) located in the dilp8 promoter. Importantly, a minimum promoter encompassing the three HREs is sufficient to activate dilp8 transcription in vitro and in vivo. We propose that dilp8 is a direct target of the Hippo pathway and its expression levels inversely correlates with organ size allowing a coupling between autonomous organ growth programs and animal maturation.

Drosophila MAGI interacts with dRASSF8 to regulate E-Cadherin based Adherens Junctions in the developing eye

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Morphogenesis is critical during development to generate organs and tissues of the correct size and shape. During Drosophila late eye development, inter-ommatidial cells (IOCs) rearrange to generate the highly organized pupal lattice, where hexagonal ommatidial units pack tightly. This process involves the fine regulation of Adherens Junctions (AJs), and of the adhesive E-Cadherin complexes. Localized accumulation of Bazooka, the Drosophila PARD3 homolog, has emerged as a critical step to specify where new E-Cadherin complexes should be deposited during junction remodeling. However, the mechanisms controlling the correct localization of Bazooka, are still only partly understood. We show here that dMagi, the sole fly homolog of the mammalian MAGI scaffolds, is an upstream regulator of E-Cadherin based AJs during cell rearrangements, and dMagi mutant IOCs fail to reach their correct position. We uncover a direct physical interaction between dMagi and the Ras Association domain protein dRASSF8, through a WW domain - PPxY motif binding, and show that apical dMagi recruits the dRASSF8/dASPP complex during AJ remodeling in IOCs. We further show that this new dMagi complex is required for the cortical recruitment of Bazooka, and of the E-Cadherin-associated proteins a- and b-catenins. We propose that, by controlling the proper localization of Bazooka in remodeling junctions, dMagi and the dRASSF8/dASPP complex promote the recruitment or stabilisation of E-Cadherin complexes at junction sites.

Characterization of the Drosophila hematopoietic niche: role of the Slit/Robo signaling pathway

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Vertebrate Hematopoietic Stem Cells (HSCs) are responsible for lifelong maintenance of the blood system. Deregulation of the hematopoietic differentiation program is at the origin of numerous pathologies including leukaemia. Maintaining HSCs depends on signals provided by their micro-environment called the « niche ». Many studies have underlined the complexity of the cellular communication between HSCs and the niche. The discovery of a niche, called the Posterior Signaling Center (PSC), responsible for maintaining a pool of hematopoietic progenitors in the Drosophila hematopoietic organ, the lymph gland (LG), has made Drosophila a model with witch to investigate this communication (Krezmien et al., 2007 ; Mandal et al., 2007). It was recently shown that the number of niche cells must be tightly controlled by the BMP/Dpp and Wg pathways, in order to maintain blood cell homeostasis (Pennetier et al., 2012). Starting from transcriptome analyses of LGs, we observed that Robo receptor is expressed in the PSC and its ligand Slit in the cardiac tube beneath the LG. Loss of Slit/Robo activity leads to an increased number of PSC cells and loss of their adhesive properties. We show that the Slit/Robo pathway controls the proliferation of PSC cells regulating the BMP/Dpp pathway activity in PSC and cohesion of PSC cells by modifying the activity of the small GTPase Cdc42. Finally, the Slit/Robo signalization interferes with DE-Cadherin to regulate both the proliferation and loss of cohesion of PSC cells. Our data thus provide evidence for the key role that communication between the cardiac tube (aorta) and the niche plays in preserving niche integrity.

p53-dependent necrosis suppresses tumorigenesis in Drosophila

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The functions of the tumor suppressor p53, which is mutated in 50% of cancers, include DNA repair, cell cycle arrest and apoptosis. Recent evidences have suggested that p53 regulates also necrotic cell death, which is implicated in several pathologies, such as cerebral stroke and myocardial infarction. However, the role of p53 in the regulation of necrosis and its in vivo contribution remain unknown. Here, we examined the role of p53 in germ cell death (GCD), a pathway of necrotic cell death that regulates tissue homeostasis during Drosophila spermatogenesis. We found that p53 mutant testes exhibited a reduced GCD, as other mutants of the necrotic pathway. Furthermore inhibition of GCD promoted tumor-like formations in the adult testes. I will present further characterization of p53-dependent necrosis and discuss its importance as a tumor suppressive mechanism during development.

Human Tau expression during Drosophila development strongly affects mitotic progression and chromosome segregation

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The cortex of Alzheimer's disease (AD) brains is marked by amyloid plaques and Tau tangles and it contains increased numbers of cell death-prone aneuploid neurons. To date, the origin and pathogenic relevance of aneuploidy in AD remain poorly understood. In the last decade, several models to study the mechanisms involved in Alzheimer's disease progression have been developed in Drosophila melanogaster. It has been shown that human Tau expression in Drosophila induced adult onset neurodegeneration through neuronal postmitotic cell cycle re-entry and cellular death. However, the effect of human Tau expression during Drosophila development has not been well characterized. Thus, we quantified the neurodegeneration induced by human Tau expression in photoreceptors during development versus adulthood. Interestingly, our results illustrate that only developmental expression of human Tau induces adult onset neurodegeneration. Then, we performed a forward genetic screen to identify modifiers of Tau pathology during development in the eye disc. Our results identified numerous genes with established functions in cell cycle and mitotic spindle regulation suggesting that the visible adult eye phenotype originate during development. Next, we investigated in more detail cell cycle progression upon human Tau expression in both the eye disc and in larval neuroblasts. Our results show that human Tau expression strongly affect mitotic progression and chromosome segregation. In both models, Tau expression induces a mitotic delay characterized by the formation of monopolar spindles, circular figures, hypercondensed chromosomes and desynchronized anaphase resulting in severe aneuploidies in progenitor and daughter cells. Taken together, we propose that Tau-mediated neurodegeneration is in part linked to mitotic spindle and chromosome segregation defects during neuronal proliferation.

Neuronal expression of mitochondrial uncoupling proteins increases oxidative stress resistance and protects against functional senescence in Drosophila

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Accumulation of oxidative damages and reduction of antioxidant defense systems in cells play a key role in functional and organismal senescence, as well as in neurodegenerative diseases. Increased ROS production from defective mitochondria promotes accelerated aging and the onset of neurodegeneration. Therefore, controlling ROS production in neurons could be relevant to longevity and healthspan. The uncoupling proteins (UCPs) are proton carriers and ROS modulators associated to the mitochondrial internal membrane. Here we examined the potential protective roles of UCPs against age-related locomotor decline and oxidative stress in the Drosophila model. Using various cell-specific GAL4 drivers, we expressed in vivo human and Drosophila forms of UCPs in different subtypes of neurons in the central nervous system (CNS) and monitored locomotor activity during aging with a startle-induced negative geotaxis assay. Our findings showed that the expression of human hUCP2 in dopaminergic or serotonergic neurons, but not in glutamatergic neurons, improved locomotor fitness in aging flies, leading to delayed age-related locomotor decline (ARLD). Similar results were observed by expressing hUCP2 in both the dopaminergic and serotonergic neurons. In contrast, and surprisingly, ARLD was delayed by overexpressing the Drosophila DmUCP5 in glutamatergic neurons, but not in dopaminergic or serotonergic neurons, suggesting that protection depended both on the neuron and UCP subtypes. We also showed that the cell-specific expression of UCPs, in most but not in all cases, significantly increased the resistance of Drosophila to paraquat-induced oxidative stress. This study provides evidence for ROS involvement in Drosophila ARLD and suggests that preserving mitochondrial integrity in CNS neurons could efficiently protect against functional senescence in an aging organism.

The Drosophila TNF receptor Grindelwald couples loss of cell polarity with neoplastic growth

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Disruption of epithelial polarity is a key event in the acquisition of neoplastic growth. JNK signalling is known to play an important role in driving the malignant progression of many epithelial tumours, though 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 growth1, we identified grindelwald (grnd), a gene encoding a transmembrane protein with homology to members of the tumour-necrosis factor receptor (TNFR) superfamily. We show that Grnd mediates the pro-apoptotic functions of Eiger (Egr), the unique Drosophila TNF, and that over-expression of an active form of Grnd lacking the extracellular domain is sufficient to activate JNK signalling both in flies and in human cells. Grnd also promotes the invasiveness of RasV12/scrib-/-tumours through Egr-dependent Matrix MetalloProtease-1 (MMP1) expression. Grnd localises to the sub-apical membrane domain with the cell polarity determinant Crumbs and couples Crumbs-induced loss of polarity with JNK activation and neoplastic growth through physical interaction with dLin7. Therefore, Grnd represents the first example of a TNF receptor that integrates signals from both Egr/TNF and apical polarity determinants to induce JNK-dependent cell death or tumour growth.

Study of resilience and proteostasis during intestinal infections in Drosophila

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Host defense encompasses two complementary facets: resistance and resilience. The first one corresponds to the attack of the pathogen by the immune system, whereas the latter one illustrates the ability of the host to endure and repair damages after infection.
Upon oral infection with the opportunistic bacteria Serratia marcescens, an unexpected cellular process takes place at the level of the gut epithelium. In response to the pore-forming toxin hemolysin secreted by the bacteria, the cytoplasm and damaged organelles of enterocytes are partly extruded into the lumen in the absence of any lysis and cell death, thus yielding a remarkably thin epithelium. In only a few hours, the fly intestinal epithelium is completely regenerated as the enterocytes recover their full volume.
The regeneration of enterocytes entails the reconstitution of components that have been lost during extrusion: mitochondria and metabolites such as proteins, lipids or carbohydrates. RNA-seq analysis revealed the induction of tens of genes induced at the gut level after infection, including a gene encoding an amino-acid transporter. This transporter is required for the rapid regeneration of the gut and is located on the basal side of the intestinal epithelium. Several other amino-acid transporters were found to be also important for the recovery. Moreover, the regeneration involves the retrograde transport of amino-acids from the rest of the organism to the gut epithelium and not from the lumen to the epithelium. Processes such as autophagy and/or the proteasome pathway will need to be analysed in the other body organs or tissues. This work will lead us to study: i) the role of the TOR pathway in the regeneration and ii) the involvement of our candidate amino-acid transporter in the activation of this pathway. Finally, some preliminary data encourages us to study further the implication of lipids in the recovery phase.

Mechanisms underlying Lactobacilli-mediated juvenile growth promotion: "learning on the fly"

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It is now commonly admitted that microbiota, and more particularly intestinal bacteria impacts its host physiology. Our group showed that the fly commensal bacterium Lactobacillus plantarum promotes larval growth of Drosophila melanogaster under nutrient deprivation by genetically acting upstream of the host TOR-dependant nutrient sensing system. However, the genetic architecture underlying the host/commensal bacteria interaction is still to be unravelled. In this study we sought to determine how genomic variations impinge on the growth benefit sustained by L. plantarum. To answer that question, we assayed the growth benefit of L. plantarum among different fly genetic backgrounds: we used 53 lines from the Drosophila melanogaster Genetic Reference Panel (DGRP) using the 7-day old larval size as readout. Our results showed that 1) L. plantarum benefits growth of all the lines we tested and 2) The response to the bacterium is very variable among the lines. So our work brings stronger evidence that genomic variations impinge on the growth benefit sustained by gut commensals. We will present the first GWAS results obtained with this dataset and our ongoing efforts to functionally validate the identified candidate genes.

Rôle de la voie des piARN dans la régulation des ARN messagers maternels

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Le passage d'une cellule unique, à un organisme multicellulaire organisé selon un axe, nécessite de nombreux mécanismes moléculaires importants. Un de ces mécanismes est la création de gradients de protéines dans l'embryon permettant de déterminer un axe de développement. Ces protéines appelées morphogènes vont donc déterminer l'orientation des premières divisions cellulaires. Ce gradient de morphogènes est réalisé par de nombreux processus dont la régulation de la stabilité des ARN messagers (ARNm) maternels. En effet dans les premières heures du développement
le génome embryonnaire n'est pas transcrit et ce sont donc les ARNm présents dans l'ovocyte qui vont créer ce gradient. La régulation de la stabilité des ARNm est elle aussi modulée par de nombreux mécanismes. Un de ceux ci a été découvert récemment dans le laboratoire de M. Simonelig. Ils ont montré que des petits ARN sont capables de déstabiliser l'ARNm de nanos afin de créer un gradient de protéines dans l'embryon précoce de Drosophile. Ce morphogène conservé chez l'homme est détruit dans l'embryon sauf à l'extrémité postérieur où il va être accumulé afin de déterminer l'axe de développement. Ils ont aussi montré que ces petits ARN étaient issus de la transcription d'éléments transposables. Pendant très longtemps ces éléments ont été considérés comme des parasites ou de l'ADN poubelle,or l'équipe de M. Simonelig a démontré qu'ils avaient un rôle dans une des étapes clefs du développement embryonnaire. Il existe donc une coévolution entre les éléments transposables et le génome hôte afin de réguler finement certains ARNm. Cependant les protéines impliquées dans cette régulation sont aussi présentes au pôle postérieur de l'embryon et pourraient donc déstabiliser l'ARNm de nanos. Il semblerait donc qu'un changement dans la régulation a lieu dans cette localisation et que ces petits ARN aient un rôleprotecteur des ARNm maternels.

"piRNA-mediated repression during Drosophila development"

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piRNA-mediated repression during Drosophila development
Maintaining the genome integrity is particularly important in the germline which transmits the genetic information over generations. The activity of transposable elements in animals is regulated by small non-coding RNAs associated with PIWI family proteins (piRNAs). This regulation has extensively been studied during Drosophila gametogenesis, but very little is known about piRNA-mediated silencing during the germline development. Indeed, maintenance of genome integrity over generations requires that regulation takes place throughout the entire life of germ cells.
We investigate the functional and molecular properties of the piRNA-mediated repression during Drosophila development. We have established the existence of a functional repression during all larval stages as well as in pupae. Using the TRIPlines (modified miRNA), we show that most of all the known partners of the piRNA pathway in the adult are also necessary during development. Moreover we analyze an incomplete silencing discovered in adult ovaries that we call variegation. We show that this phenomenon takes place during development as well. Is this a developmental epigenetic memory that exists throughout germline development or a fluctuating state is the question that we plan to answer.
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Epigenetic control of ribosome biogenesis: deciphering the role of RPL12 in transcription.

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In Drosophila, the Enhancer of Trithorax and Polycomb Corto binds chromatin via a chromodomain, and is involved in epigenetic control of gene expression. While canonical chromodomains recognize tri-methylated lysines on histone tails, the Corto chromodomain binds a ribosomal protein: RPL12. Moreover, this interaction occurs through specific recognition of RPL12 lysine 3 tri-methylated (RPL12K3me3). Corto and RPL12 share many sites on chromatin and RNA-seq experiments suggest that they regulate a subset of genes involved in ribosome biogenesis (Ribosomal Protein and Ribosomal Biogenesis genes) (Coléno-Costes et al., 2012). Our results suggest that the tri-methylation of RPL12 on lysine 3 controls its transcriptional activity. To identify RPL12 and Corto transcriptional targets, we generated transgenic lines allowing expression of the Corto chromodomain, RPL12 or a RPL12 variant whose lysine 3 is replaced by alanine (RPL12K3A). We are currently analyzing their transcriptome by RNA-seq as well as the genome-wide binding of RPL12, RPL12K3A and Corto by ChIP-seq. To question the role of RPL12 tri-methylation in its physiological context, we are generating a RPL12K3A mutant by using the CRISPR/Cas9 technology.

Genome wide identification of cis-regulatory elements from (very) small cell population: Insights from the drosophila cardiac tube.

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Decrypting tissue specific gene expression regulation and cis-regulatory circuits is a central issue to understand organogenesis. To get an holistic view of the regulatory landscape at play requires the acquisition of genome-wide informations. However generating tissue-specific genomic data from scarce cell populations in the developing embryo remains a big challenge.
To address this we focused on the developing cardiac tube, being made up of only 104 myocytes representing less than 0,5% of the whole embryo, while focusing more precisely on cardioblasts diversification and differentiation, the latest steps of heart organogenesis.
Chromatin modifications are associated with different aspects of gene expression including enhancers and promoters activity states. Using a highly specific cardiac reporter, we adapted a recently described method for cell type specific analysis of chromatin states (BITS-ChIP-seq; Bonn et al, 2012) to very rare cell populations. We identified cardioblasts-specific active enhancers and promoters by analysing two histone modifications (H3K27ac and H3K4me3) at a genome wide scale. In addition, to analyse heart specific gene expression levels we also generated RNA-seq data from FACS sorted cardioblasts. In silico and in vivo validations confirmed the accuracy and specificity of our data. Finally we are using machine learning approaches with these genomic data to detect the main features of cardiac specific enhancers with the aim of getting new insights regarding the gene regulatory network governing cardioblasts differentiation.

Pri peptides are mediators of ecdysone for the temporal control of development

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Animal development fundamentally relies on the precise control, in space and time, of genome expression. While we have a wealth of information about spatial patterning, the mechanisms underlying temporal control remain poorly understood. Here we show that Pri peptides, encoded by small-ORFs, are direct mediators of the steroid hormone ecdysone for the timing of developmental programs in Drosophila. We identify a previously uncharacterised enzyme of ecdysone biosynthesis, GstE14, and find that ecdysone triggers pri expression to define the onset of epidermal trichome development, through post-translational control of the Shavenbaby transcription factor. We show that manipulating pri expression is sufficient to either put on-hold or induce premature differentiation of trichomes. Furthermore, we find that ecdysone-dependent regulation of pri is not restricted to epidermis and occurs over various tissues and times. Together, these findings provide a molecular framework to explain how systemic hormonal control coordinates specific programs of differentiation with developmental timing.

An Org-1--Tup transcriptional cascade reveals the existence of different types of alary muscles connecting internal organs in Drosophila

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The T-Box transcription factor Tbx1 and the LIM-homeodomain transcription factor Islet1 are key components in regulatory circuits that generate myogenic and cardiogenic lineage diversity in chordates. We show here that Org-1 and Tup, the Drosophila orthologs of Tbx1 and Islet1, are co-expressed and required for formation of the heart-associated alary muscles (AMs) in the abdomen. The same holds true for lineage-related muscles in the thorax that have not been described previously, which we name TARMs.3-dimensional high resolution analyses indicate that AMs and TARMs connect the exoskeleton to the aorta/heart and different regions of the midgut, respectively, and border specific tracheal branches, pointing to an architectural role in the internal anatomy of the larva. Org-1 controls tup expression in the AM/TARM lineage, by direct binding to two regulatory sites within an AM/TARM-specific cis-regulatory module, tupAME. The contributions of Org-1 and Tup to the specification of Drosophila AMs and TARMs provide new insights into the transcriptional control of Drosophila larval muscle diversification and new parallels with Gene Regulatory Networks involved in specification of cardiopharyngeal mesodermal derivatives in chordates.

The Atypical Cadherin Dachsous and Planar Cell Polarity control Left-Right Asymmetry in Drosophila

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Stereotyped left right (LR) asymmetry ensures proper looping of internal organs. In Drosophila, the adult hindgut (AHG) has a clear stereotypical dextral loop and, like all LR asymmetric organs, require MyoID for correct orientation. MyoID is an unconventional myosin type I that binds to DE-Cadherin, this association is required for proper LR establishment; however the mechanism that translates MyoID chirality into proper morphogenesis remains unknown.
The AHG is a long tube coiled dextrally and located in the middle of the abdominal region. It develops from a cluster of progenitors containing two different populations of cells, H1 and H2. Here, we show that MyoID controls the AHG dextral loop by binding to the atypical cadherin Dachsous in H1 cells. Further, Ds-Fat signaling propagates towards the H2 cells which in turn become polarized towards the right and consequently loop. H1 is a transient population of cells that wear off in the first hours of metamorphosis; nevertheless the dextral information generated in H1 is maintained in H2 cells due to the cooperative action of PCP components. We demonstrate that the molecular basis of the LR establishment downstream of MyoID action lies in the PCP system, which has a double role transmitting and maintaining a dextral signal in the AHG. Thus, we provide for the first time a link in LR morphogenesis between Drosophila and vertebrates in which PCP mutants result in LR defects.
Furthermore, in our attempts to better understand the evolution of L/R morphogenesis we found the recently co-appearance of a myoID genetic regulatory element and the AHG dextral loop, during Drosophila evolution, suggesting that changes in myoID expression pattern induced the evolution of asymmetric structures.

The transcription factor Shavenbaby controls drosophila renal stem cells behaviour

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Throughout adult life, the homeostasis of fundamental functions requires organ renewal to compensate for tissue damage and cell death. Recent work has demonstrated the key role of adult stem cells in organ regeneration. To achieve replacement of differentiated cells in the adult organ, adult stem cells must reactivate, at least in part, the molecular pathways used to build functional organs during embryogenesis. However, little is known on which and how embryonic regulatory networks become reactivated to regulate the proliferation and differentiation of adult stem cells. We have shown that the transcription factor, Shavenbaby (Svb), is both expressed and required to control adult renal stem cell behaviour. During embryonic development, under the action of Wingless, Notch, EGF and Hedgehog pathways, Svb activates the expression of cell effectors to specify which subset of epidermal cells form apical extensions called trichomes. The transcriptional activity of Svb is controlled by Pri (polished rice) peptides allowing its maturation from a repressor to an activator. Exploiting the knowledge and functional tools available, my aim is to unravel the function of the Shavenbaby network and identify novel interactors in adult kidney stem cells homeostasis.

Function and regulation mode of the pri gene during drosophila development

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Cell morphogenesis is an essential process during development, required for cells to acquire their function. During drosophila development, epidermal cells undergo morphogenesis and form apical protrusions called trichomes. Shavenbaby, a zinc finger transcription factor, has been identified as necessary and sufficient to orchestrate trichome formation. The discovery of sORFs (short Open Reading Frames) gave the opportunity to identify Polished rice (Pri), small peptides, that turn on Shavenbaby function through a post translational elimination of its N-terminal end. The pri gene displays a very dynamic profile in various tissues such as epidermis, trachea and leg along development. To better understand the function of pri gene, we aim to determine cis regulatory regions and trans factors allowing its dynamic and specific expression. We recently showed that the ecdysone pathway controls pri expression. Ecdysone is an ecdysteroid hormone that controls the timing of important developmental transitions. Pri peptides constitute a component of ecdysone pathway and mediate the temporal control of development. We detailed in epidermis how pri integrates the ecdysone pathway activity. We are searching now whether Pri peptides exert a temporal control of other differentiation programs such as trachea and leg morphogenesis through mechanisms already defined for the epidermis. We will thus molecularly define how Pri peptides mediate the systemic action of ecdysone to synchronize developmental programs among tissues.

Extrinsic DRL Guides DRL-2-expressing Drosophila Mushroom Body Axons by WNT5 Ligand presentation and Ectodomain Shedding

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In vivo axon pathfinding mechanisms in the neuron-dense brain remain relatively poorly characterized. Neurons often innervate multiple distinct targets via axon branching, however, how differential guidance of branched axons occurs remains unclear. We study the Drosophila mushroom body (MB) axons whose ? and ? branches target different brain structures. We show that the Ryk family WNT5 receptor, DRL (derailed), expressed in the developing central complex, is required for MB ? branch axon guidance. DRL acts to capture and present WNT5 to MB axons rather than transduce a WNT5 signal since DRL's cytoplasmic domain is not required. Supporting this, WNT5 is delocalized from its normal sites in drl mutant brains. DRL's ectodomain (ECD) must be cleaved and shed to guide ? axons. DRL-2, another Ryk, is expressed within MB axons and functions as a repulsive WNT5 signaling receptor. Finally, our biochemical data support the existence of a ternary complex composed of the cleaved DRL ectodomain, WNT5 and DRL-2. Thus, the interaction of MB-extrinsic and -intrinsic Ryks, via their common ligand, acts to guide MB ? axons. To the best of our knowledge, this is the first description of such a mechanism in the developing adult brain where the capture and localization of a widely-expressed repulsive ligand to the surfaces of nearby cells ensures the guidance of axons required to form a distinct brain structure. Also, the formation of a ternary complex by a shed ECD, the ligand and an axon-intrinsic receptor may likely prove to be conserved developmental strategies.

Neuroendocrine Control of Drosophila Behavior

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In multicellular organisms, secreted hormones modulate the physiology and behavior of distant organs, and this regulation includes the Central Nervous System (CNS). At the same time, the CNS directs animal responses to different environmental cues. How hormones can affect neuronal activity and how both actions are coordinated to maximize chances of survival is still poorly understood. In the past decade, Drosophila melanogaster has emerged as a simple model to combine neurobiological and behavioral approaches. Here, we show that the prothoracicotropic hormone (PTTH), a neuropeptide that controls the developmental transition from juvenile stage to sexual maturation, also regulates light avoidance in Drosophila larvae. PTTH, through its receptor Torso, acts on two light sensors 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. Surprisingly, PTTH is also expressed in the Ellipsoid Body (EB) of the adult fly brain, an important decision-making center homologous to the mammalian Globus Pallidus. This suggests a role for PTTH as a possible molecular mediator of some of the EB-regulated behaviors previously described. More interestingly, the expression pattern of its receptor torso might get some insight into the EB target neurons/tissues that are ultimately responsible for different adaptive behaviors, like memory and nutrient selection. PTTH is an example of how a hormone can regulate animal physiology and behavior at different developmental stages and at different organ levels.

Precocious divisions promote self-renewal of sensory organ precursor cells

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Developmentally regulated cell cycle arrest is a fundamental feature of neurogenesis, however its significance is poorly understood. Growing evidence also links defects in regulation of neural quiescence to neurodegenerative disease and tumour formation. To study this phenomenon we examined how G2/M timing is coordinated with cell fate specification during thoracic sensory organ development. Phenotypic analysis and time-lapse imaging of the lineage showed that forcing sensory organ precursor cells to divide prematurely resulted in supernumerary external sensory organ cells. These supernumerary cells did not arise from cell fate transformations or failure to properly segregate cell fate determinants. Instead, G2 phase quiescence ensures that precursor cells do not undergo self-renewal before terminal differentiation, revealing how cell cycle regulatory mechanisms are used to synchronize cell division with the acquisition of specific cell fates during neuronal development.

Decrypting the glia differentiation program

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Powerful transcription factors called fate determinants induce robust differentiation programs in multipotent cells and trigger lineage specification. These factors guarantee the differentiation of specific tissues / organs / cells at the right place and the right moment to form a fully functional organism. Fate determinants are activated by temporal, positional, epigenetic and post-transcriptional cues, hence integrating complex and dynamic developmental networks. In turn, they activate specific transcriptional/epigenetic programs that secure novel molecular landscapes. We deciphered the mechanism regulating the glial fate determinant glial cell missing (Gcm). Gcm acts as a 'time bomb' and triggers its own degradation once the glial programme is stably activated. This requires a sequence of transcriptional and posttranscriptional loops, whereby a Gcm target first affects the expression and then acetylation of the fate determinant, thus controlling Gcm levels and stability over time. Defective homeostasis between the loops alters the neuron: glia ratio and freezes cells in an intermediate glial/neuronal phenotype. In sum, we identify an efficient strategy triggering cell identity, a process altered in pathological conditions such as cancer.

Molecular mechanisms of CNS sparing in Drosophila

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Suboptimal nutrition during development can alter body proportions and have long-term consequences upon adult health and disease. In mammals, a key survival strategy for coping with nutrient deprivation in utero involves sparing the growth of the developing brain at the expense of other organs. We found that CNS sparing is also present in Drosophila, and were then able to identify the first underlying molecular mechanism. CNS sparing during development is only possible after neural stem cell like precursors (neuroblasts) have moved from dietary nutrient sensitive to insensitive modes of growth. The Anaplastic lymphoma kinase (Alk) functionally replaces the Insulin receptor and activates the Pi3K pathway in nutrient insensitive neuroblasts. Recent results identify temporal transcription factors, including Castor, as a key timing mechanism required for the InR-to-Alk transition. We will present data supporting a model for CNS sparing that integrates inputs from neuroblasts, their glial niche and systemic signals.

Split-ends : a new regulator of adult stem cells in Drosophila intestine

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Adult stem cells maintain tissue homeostasis by supplying differentiated cells while at the same time self-renewing. Here the adult Drosophila intestine is used to study molecular mechanisms that regulate the switch between stem cell state and differentiated state. We report the identification of the split-ends gene as a novel regulator of intestinal stem cells that control this switch. split-ends family genes encode conserved RNA recognition motif-containing proteins that are reported to have a role in RNA biogenesis and stem cell regulation. We show that its loss of function results in an abnormal increase in the number of stem cell-like cells associated to an increase of proliferation. This factor is specifically expressed in stem cells and progenitor cells where its function is required. These data suggest that Split-ends may acts as a stem cell regulator important for the repression of self-renewal and/or for the enhancement of the stem cell commitment. To get further in Split-ends molecular function, we have investigated the molecular signature of intestinal stem cells and progenitor cells knockdowned for split-ends, by combining genetics, cell sorting and mRNA sequencing analysis. Here, we provide a new function of spit-ends in adult stem cell regulation in the Drosophila intestine, which may also shed light on its mode of action in other developmental contexts.

The nutritional regulation of body size by the Drosophila TNF/JNK pathway.

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Nutritional availability plays a critical role in determining the final body size of an organism. In Drosophila, nutritional information is sensed locally by the fat body, an endocrine organ analogous to the vertebrate liver and white adipose tissue. The fat body in turn regulates body size by remotely controlling the levels of circulating Drosophila insulin-like peptides (DILPs) secreted by specialized Insulin-Producing Cells (IPCs) in the brain. However, the nature of the humoral signal(s) released by the fat body that communicate changes in nutritional status to the IPCs remains largely unknown. Through genetic screens targeting the fat body and the IPCs, we searched for candidate signals and receptors that modulate body size in response to nutritional availability. We identified Eiger (Egr), the Drosophila TNF-alpha homolog as a negative factor that participates in the reduction of body size in conditions of nutrient deprivation. The reduction in body size observed in animals grown in poor food conditions is significantly rescued both in Egr mutants and upon specific down-regulation of Egr in the fat body. Upon limiting amino acid levels in the food, the amount of Egr is modulated by regulating its release into the hemolymph. Interestingly, Grindelwald (Grnd), a TNF receptor recently identified in our lab, is specifically expressed in the IPCs and parallels the phenotypes seen with manipulating Egr levels. These results provide a framework in which fat body-derived Egr activates JNK signaling in the IPCs through the Grnd receptor to potentially modulate DILP levels and control final body size.

Host-microbiota interactions: Effects of Lactobacillus plantarum on Drosophila adult physiology

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Metazoans are naturally associated with bacterial communities, which establish commensalistic or mutualistic relationships with each other and with the host organism. These interactions play a crucial role in different aspects of the host physiology while providing the microbiota a nutrient-rich environment. When deregulated, the relationships can lead to pathological situations, such as inflammatory chronic disease, metabolic disorders or even cancers, and despite recent progress, the characteristics and molecular basis of the beneficial impact microbiota has on its host remain largely unknown.
In order to elucidate the fine-tuned dialogue governing the relationships between intestinal bacteria and their host, we use a system based on the association of the model organism Drosophila melanogaster with one of its natural commensals, Lactobacillus plantarum. This rather simple gnotobiotic model allowed us to reveal a growth-promoting effect mediated by L. plantarum in nutritionally challenged drosophila larvae and will now give us the ability to see whether this commensal bacteria has a beneficial role on its host physiology throughout it's entire life, by studying the effects of the association at the adult stage. We study different life history traits such as fecundity, fertility and resistance to full starvation as an indication of L. plantarum effects on the adult fly metabolism and will give you an overview of the first data.

A balance between JNK and Hippo signalling pathways maintains the cellular homeostasis of the intestine upon bacterial food poisoning

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The digestive tract is continuously subjected to multiple aggressions by virus, bacteria, toxins and chemicals present in the food. Therefore the gut lining has established a mechanism of replenishment in order to maintain the physiological function of the organ called "the gut homeostasis". Upon aggression, a complex network of signaling pathways is taking place between the different cell types, allowing the proliferation of the Intestinal Stem Cells and then the appropriate differentiation of ISCs daughter cells in order to replace the defective epithelial cells.
Among the aggressors hidden in the food, there is the bacterium Bacillus thuringiensis (Bt) that is widely used worldwide as bioinsecticides. Indeed, Bt bioinsecticides are increasingly used instead of chemical pesticides since the few years. These bioinsecticides are mainly used in organic farming and in forestry to fight against pest lepidopterans and there are also used for mosquito control either for the well being of the population or to fight vectors of human diseases such as yellow fever, chikungunya, and malaria. Consequently, the Bt bacterium is more is more present in the feed and environment.
Although the specificity of the acute toxicity of the Bt bioinsecticides has been proved since many years, with no acute toxicity observed towards non-target species ranging from bees to human, data are scarce on adverse effects that could result from chronic exposure. The question today is how far non-target organisms will be impacted by the augmentation of the use of Bt bioinsecticides?
To answer this challenge, we are using drosophila (a non-target organism) to study the impacts of Bt bioinsecticides on the gut physiology. I will present how the intestine quickly mounts physiological defences against Bt bacteria and is able to overcome a Bt food poisoning. I will also present the consequences of a prolonged exposition to Bt bioinsecticides.

Posters

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The role of EiF2? during organ sparing in Drosophila

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All organisms regulate their development according to internal genetic programmes and the availability of nutrients from the environment. During nutrient restriction (NR), animals from vertebrates to flies are able to protect the growth of critical organs at the expense of other tissues. Drosophila larvae subjected to complete amino acid restriction during the third instar shut down the growth of the body and of internal organs like the salivary glands and the fat body, whereas the growth of critical organs like the CNS is highly spared. In yeast and mammals, it is known that amino acid depletion increases free tRNA levels, thus activating the Gcn2 kinase. In turn, the translation initiation factor EiF2? is phosphorylated and this decreases general protein synthesis. We now find that, during NR, phosphorylated EiF2? levels do not change in the CNS whereas they increase as expected in non-spared organs. However, artificially increasing EiF2? phosphorylation in the CNS efficiently blocks growth during fed or NR conditions. Remarkably, the converse manipulation, inhibition of EiF2? phosphorylation in an otherwise non-spared organ such as the salivary gland is enough to activate sparing during NR. This observation indicates that, even for a non-spared organ, internal nutrients such as amino acids are not themselves limiting for growth during NR. Together, these findings also suggest that tissue-specific changes in EiF2? phosphorylation may make an important contribution to differential organ sparing.

Tubulin detyrosination regulates germ line stem cell differentiation in Drosophila

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Microtubules (MTs) are essential cytoskeletal elements composed of alpha- and beta-tubulin heterodimers. They are involved in many different functions including intracellular transport, cell motility, cell division and cell morphogenesis. One of the mechanisms that contribute to the functional diversity of MTs, involves a number of unusual posttranslational modifications. This includes a cycle of detyrosination/tyrosination, in which the C-terminal tyrosine residue of alpha-tubulin is removed by tubulin carboxypeptidase (TCP) and subsequently re-added by tubulin tyrosine ligase (TTL). Despite the fact that tubulin detyrosination has been discovered almost 40 years ago the enzyme involved in its generation remains unknown what greatly hinders functional studies. To overcome this problem we have developed an alternative approach to study the role of detyrosination. Using a cell-based assay we have found that changing the penultimate glutamate residue (-EEY) to aspartate (?EDY) completely blocks detyrosination. Since mammalian cells express multiple alpha-tubulin isoforms, we decided to take advantage of the Drosophila system where majority of the MT functions are supported by a single alpha-tubulin gene, alphaTUB84B. By using in vivo mutagenesis we have discovered that tubulin detyrosination plays an essential role in germ line stem cell differentiation. Blocking detyrosination leads to a «tumor-like» stem cell overproliferation during both spermatogenesis and oogenesis. This phenotype is highly reminiscent of mutant flies lacking the bag-of-marbles (Bam) transcription factor, which has been shown to be important for germline stem cell differentiation and entry into meiosis. In agreement, we found that in the absence of detyrosination Bam expression was strongly affected providing a potential mechanistic explanation for the observed defects. Taken together our results clearly demonstrate that tubulin detyrosination regulates gametogenesis in Drosophila.

Role and expression of the amino acid transporter heavy chain CD98hc in Drosophila melanogaster

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Animals use many sensory modalities to decode environmental cues in order to find for example a source of food, including vision, taste, or olfaction. These signals are detected in peripheral sensory systems and integrated into the brain where they trigger an appropriate behavioral response. To understand how the nervous system works is necessary to better interpret complex behaviors such as olfaction.
Amino acids, such as glutamate, are crucial for proper functioning of the nervous system. These amino acids are transported via different systems. One of them consists of the heterodimeric amino acid transporters (HATs). The HATs consist of a light chain, which allows the specificity of amino acids transport and a heavy chain involved in plasma membrane insertion. Studies on two light chains : Genderblind and Minidiscs suggest that HATs may be involved in Drosophila olfactory perception. These light chains potentially share the same heavy chain : CD98hc. The role of CD98hc gene in olfaction was carried out by inactivating this gene using siRNA expressed in neuronal or glial cells. The olfactory response was studied in adults using behavioral tests that measure the detection of food medium. Our data indicates that the heavy chain CD98hc is involved in olfactory perception in Drosophila. We also found that CD98hc is expressed in different regions of the central nervous system including some involved in olfaction (cortex glia close to antennal lobes, and neurons of mushroom body calyces -secondary olfactory centers-). Altogether, our results suggest that expression of CD98hc in glial cells and neurons is required for the integration of chemosensory stimuli in the central nervous system.

Role of Dystrophin/Dystroglycan during tissue elongation of ovarian follicles

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Tissue elongation is a process of the morphogenetic repertoire essential for development. In Drosophila ovarian follicle, elongation involves the planar polarization of the follicular epithelium basal domain and the formation of polarized extra-cellular matrix (ECM) fibers. These fibers form a molecular corset that is proposed to constrain the medio-lateral growth of the follicle and so promote its elongation. We identified in Dystrophin and Dystroglycan mutants an elongation defect associated with a complete absence of ECM fibers. Characterization of Dystrophin localization has revealed that it is planar polarized and, this, very early during follicle development. It provides the earliest marker of planar polarity described so far in this tissue. Furthermore, Dystrophin localization is concomitant with ECM fibers deposition and is similar to the one of secretion vesicles containing collagen. Together, these results suggest a direct function in ECM secretion for Dystrophin and Dystroglycan. Moreover, Dystrophin localization requires the F-actin, which is sometimes locally affected in dystroglycan mutants, suggesting an interdependence between Dystroglycan and actin fibers. The planar polarized orientation of the actin fibers is known to be controlled by the atypical cadherin Fat2 whose mutants show a global defect of this orientation but in which Dystrophin can still be planar polarized. This allows us to propose the existence of two parallel basal planar cell polarity pathways : one, global, controlled by Fat2, and another, local, controlled by the Dystrophin-Dystroglycan complex. Future experiments will show which function of Dystrophin/Dystroglycan, the production of ECM fibers or the planar polarization of F-actin fibers, is determinant for tissue elongation.

Deciphering the hematopoietic niche with Drosophila

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Hematopoietic Stem Cells (HSCs) are responsible for generating all blood cells throughout life. In adult mammals, hematopoiesis takes place in the bone marrow. Maintaining HSCs in the bone marrow is dependent on a specific micro environment called the «niche». The cellular and molecular processes involved in the communication between the HSCs and the niche are very complex and poorly understood. In Drosophila larvae hematopoiesis takes place in a specialized organ called the lymph gland (LG). The LG is composed of three zones: (1) the medullary zone (MZ) that contains the hematopoietic progenitors called pro-hemocytes (2) the cortical zone (CZ) containing the differentiated hemocytes and (3) the Posterior Signaling Center (PSC). Several independent studies have established that the PSC is required to maintain the balance between pro-hemocytes and differentiated hemoyctes, establishing that the PSC has as a role equivalent to the hematopoietic niche in the vertebrate bone marrow. Studying PSC's functions in Drosophila constitutes an interesting model to decipher in vivo the function of a niche. To identify new genes expressed in the PSC, transcriptomic analyses on dissected LGs, from different conditions and at two developmental time points, were performed. A cross comparison of these transcriptomes allowed us to establish a list of 80 genes potentially expressed in the PSC. To determine if they are involved in LG hematopoiesis, I undertook a functional analysis by performing systematic RNAi analysis in PSC. Among the 80 genes tested, 12 show a defect either in the formation of the PSC and/or in the number of pro-hemocytes and differentiated hemocytes. These 12 genes are classified in seven phenotypic classes, illustrating the high complexity of the PSC function. I am currently characterising in more detail the functions of 4 genes representative of 3 classes of phenotype.

Social transmission of a mate preference in Drosophila melanogaster

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Mate choice is a major fitness-affecting decision in sexually reproducing organisms. To select a mate organisms gather information, for instance, by copying the mate choice of conspecifics (ie mate copying). If females learn the general rule of preferring males with similar traits, accordingly to the preference of the majority, the mating preferences may transfer across individuals and generations, thus potentially leading to cultural transmission.
Our goal was to test these points using Drosophila melanogaster. Based on the previous study of Mery et al (Current Biology, 2009) we first created a new demonstration design to make it more compatible with what could happen in nature. Then we tested if the flies were able to generalize the preference to a male trait and finally if they could copy the phenotype preferred by the majority.

Modeling Trauma-Induced Sepsis in Drosophila

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Sepsis is a life-threatening clinical condition which involves a profound systemic response to infection and results in serious, often irreversible, damage to one's own cells and tissues. Pre-existing acute inflammatory state appears to play a seminal role in sepsis occurrence. Despite being a common cause of death in hospitalized patients worldwide, little is known regarding the mechanisms at play and therapeutic strategies are lacking. This is mainly due to the complexity of this syndrome and to the difficulty of addressing how inflammation and infection interact at a systemic level in mammalian models. We therefore decided to set up a model of sepsis in drosophila, which shares a number of common innate immune pathways with mammals.
In our experimental set up, a trauma is first induced by an aseptic wound, and flies are subsequently infected with Pseudomonas Entomophila (so called double hit challenge). Compared to septic challenge alone, the survival of wounded flies is severely compromised, indicating that flies that have received the inflammatory hit are more susceptible to an infection. This suggest that, as in mammals, injury compromise the organism response to an infection.
We currently analyse the global genomic response to double hit challenge throught transcriptomic analysis. In addition, this experimental model will allow genetic susceptibility to Trauma Induced Sepsis to be analysed using the Drosophila Genetic Reference Panel (DGRP) resource. This will hopefully allow a system level understanding of the mechanisms underlying sepsis in flies.

The Drosophila melanogaster Rh50 protein is required for normal structure and activity of the neuromuscular system

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The Rh50 proteins belong to the Rhesus (Rh) family, which notably comprises the proteins carrying the human Rhesus blood group antigens. Rh50 proteins, together with methylammonium permeases (MEP) and ammonium methylammonium transporters (AMT), constitute the superfamily of the ammonium transporters. We recently observed that the only Drosophila melanogaster Rh50 homologue (DmRh50) is expressed in the larval muscles and enriched in the postsynaptic membrane of the neuromuscular junction (NMJ). Targeted inactivation of DmRh50 in muscle cells by RNA interference disrupted the structure of muscles and NMJs in third instar larvae, and induced lethality during the pupal stage. Further experiments showed that the downregulation of DmRh50 in muscles leads to a thinner and elongated larval musculature, a reduced number of a specific type of synaptic boutons (Is) at the NMJ, and a strong defect in larval locomotion. By immunocytochemistry labeling of the larval body wall muscles, we observed that DmRh50 could be associated to other proteins, such as discs-large (DLG), that are required for the structural and functional integrity of the NMJs. Therefore, our results suggest that Rh50 has both a structural and physiological function in the Drosophila neuromuscular system.

A deficiency screen to identify gene networks underlying developmental stability.

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Developmental stability, the buffering of developmental noise, is of paramount importance to maintain symmetry in bilaterians. Indeed, noisiness in processes controlling organ size causes imperfect symmetry. Hence, noise can be estimated by fluctuating asymmetry (FA), the random deviation from perfect symmetry within a population. We have shown that overexpression of Cyclin G (CycG) induces up to 40-fold increase of FA, particularly visible for the wings, suggesting that CycG is involved in developmental stability (Debat et al. 2011 PLoS Genetics, 7, e1002314). Interestingly, CycG-induced asymmetry in wing shape was qualitatively very similar to that observed, although at much lower levels, in wild type flies, indicating that the developmental processes impaired are likely those that normally ensure stable development. Hence, CycG overexpression is an appropriate tool to tackle the up to now little known genetic bases of developmental stability.
Taking advantage of the extreme wing FA phenotype induced by CycG overexpression, we have performed a genome-wide deficiency screen for FA modifiers, using 509 strains with overlapping deficiency that uncover 98% of the euchromatic Drosophila melanogaster genome. Each deficiency was associated with the CycG gain of function context that induces high wing size FA. Potential modifiers of CycG FA were identified by comparison of wing length FA observed in populations of CycG overexpressing flies that carried or not a deficiency. We found that about 10% of the deficiencies significantly modified FA after Bonferroni-Holm correction, acting either as suppressors or as enhancers of high CycG-induced FA. We will present overall results of the screen, along with examples of CycG FA modifying deficiencies, and discuss their potential implication in symmetry maintenance and the buffering of developmental noise.

Molecular and functional analysis of cardiac diversification by cell specific genome approaches

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Our current knowledge on the genetic control of normal and pathological heart development is basically founded on the functional analysis of individual genes.
Cardiac cells diversification goes with numerous changes in the expression of a repertory of genes that allow cells to acquire their own identity and functions. The goal of this project is to understand the genetic pathways that control the formation of different types of cardiac cells by applying new technological developments involving whole genomic approaches in cell type resolution that we can use in Drosophila model. The Drosophila embryo is a relatively simple model to study the diversification of cardiac cells and their properties. Only three types of cardioblasts exist in early embryogenesis and even after anteroposterior differentiation the various cell types are easily identifiable. Our goal is to identify the transcriptome specific to each type of cardiac cells and the mechanisms of transcriptional regulation, basics of the process of heart cells diversification.
The main objectives in this project are: 1) Perform cell-specific translatomic analyses in subsets of three populations of Drosophila cardiac cells, at three different time windows, by applying the Translation Ribosome Affinity Purification (TRAP) method and RNA sequencing, 2) identify cardioblast specific and stage specific translated mRNA. According to the results already obtained in the team, TRAP seems to be efficient to identify transcriptional signatures in different subsets of cells. 3) Perform cell-specific chromatin immunoprecipitation experiments and identify direct targets of cardiac identity genes. 4) Analyse expression and functions of identified candidate genes and build networks of genes controlling the acquisition of individual properties and model the process of cardiac diversification.

The Drosophila TNF receptor Grindelwald couples loss of cell polarity with neoplastic growth

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Disruption of epithelial polarity is a key event in the acquisition of neoplastic growth. JNK signalling is known to play an important role in driving the malignant progression of many epithelial tumours, though 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 growth1, we identified grindelwald (grnd), a gene encoding a transmembrane protein with homology to members of the tumour-necrosis factor receptor (TNFR) superfamily. We show that Grnd mediates the pro-apoptotic functions of Eiger (Egr), the unique Drosophila TNF, and that over-expression of an active form of Grnd lacking the extracellular domain is sufficient to activate JNK signalling both in flies and in human cells. Grnd also promotes the invasiveness of RasV12/scrib-/-tumours through Egr-dependent Matrix MetalloProtease-1 (MMP1) expression. Grnd localises to the sub-apical membrane domain with the cell polarity determinant Crumbs and couples Crumbs-induced loss of polarity with JNK activation and neoplastic growth through physical interaction with dLin7. Therefore, Grnd represents the first example of a TNF receptor that integrates signals from both Egr/TNF and apical polarity determinants to induce JNK-dependent cell death or tumour growth.

Role of the JNK signaling pathway in developmental cell reprogramming

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The JNK signaling pathway plays a role in cell reprogramming to pluripotent stem cells in vitro, as well as in regeneration and transdetermination in Drosophila. Our laboratory showed that JNK activity is also important in a developmental context to induce a unique cell reprogramming event occurring in the ectoderm during dorsal closure (DC) of the fly embryo (Gettings, Serman et al., Plos Biology 2010 8(6):e100039). DC consists of the migration of the two lateral ectodermal sheets and their perfect fusion at the dorsal midline. JNK, activated in the leading edge (LE) of the migrating ectoderm, is essential for DC to proceed. Fourteen segments compose the embryonic ectoderm, each one being divided in an anterior compartment with cells expressing patched, and a posterior compartment with cells expressing engrailed. We identified anterior cells, called the mixer cells (MCs), localized at the intersection between the LE and the segment boundary, being therefore JNK and Patched positives, and Engrailed negatives. During DC, MCs cross the segment boundary, integrate the adjacent posterior compartment and just before they are reprogrammed to express de novo engrailed in a JNK-dependent manner. We are currently focusing on a link between JNK, reprogramming and the PcG (Polycomb Group) genes, a family of silencing genes acting on the chromatin structure. Polycomb, a gene belonging to the PcG gene family, is necessary for JNK to induce the mixing. However, in contrast to what we expected, Pc had a positive role on cell mixing, arguing against a negative role of Pc on engrailed expression. We are currently investigating the molecular mechanisms of the action of JNK pathway and Pc at the engrailed promoter. We hope that this work will bring new insight to cell reprogramming that occurs during normal development, and will also provide new avenues for better understanding regeneration and reprogramming-related pathologies.

Small peptides induce selective ubiquitination to activate the transcription factor Shavenbaby by proteasome protein processing

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Recent studies based on bio-informatics and ribosome profiling experiments revealed that a wide variety of RNAs contain small Open-Reading-Frames (smORFs) in yeast, invertebrates and mammals. However, the existence and the putative mode of action of smORF-encoded peptides remain elusive in the absence of direct evidence. The Drosophila polished rice/tarsaless (pri/tal) gene encodes smORF peptides that control developmental processes. We previously showed that Pri peptides switch the transcriptional activity of Shavenbaby (Svb), a transcription factor required for epidermal differentiation. Here we demonstrate that Pri peptides induce a proteasome-mediated protein processing of Svb. Genome-wide RNAi screening identified the E3 ubiquitin ligase that targets, in a pri-dependent manner, Svb to the proteasome, which limited degradation ensures processing. As shown in vitro using synthetic peptides, we find that Pri peptides promote the binding of the E3 ligase to the Svb Nterminus. This in turn triggers ubiquitination of the Svb N-term degron and proteasome processing to release the activated form of the Svb transcription factor. Genetic ablation further demonstrates that this E3 ligase is essential for Svb processing in vivo and therefore for epidermal differentiation. These mechanistic insights into the action of Pri smORF peptides show how such small compounds can control proteasome action and, thereby, the execution of developmental programs.

Toward a functional characterisation of Drosophila adult haematopoietic system.

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Abstract : Reminiscent of the vertebrate myeloid lineages, Drosophila blood cells play an important role in the innate immune response. Whereas Drosophila blood cells have been extensively studied during embryonic and larval development, the adult haematopoietic system is comparatively largely understudied despite its potential role in a number of disease and aging-related mechanism. Using a combination of larval and embryonic drivers specific to the three known haemotopoietic lineages - plasmatocytes, lamellocytes and crystal cells - we aim at carefully re-examining the origin, organisation and diversity of the adult haematopoietic system reported by others as constituted of a fixed non-proliferating pool of plasmatocytes inherited from the larva. Our preliminary results suggest indeed a more complex picture than previously assumed as crystal cell and prohaemocytes reporters are found co-expressed in a subset of cells expressing respectively the pan-haemocyte reporter *serpent* or the plasmatocyte reporter *Cg25*. Once better characterised, we will investigate the specific roles of the different sub-populations of haemocytes using transcriptomic approaches and functional assays as well as characterise the function of selected candidate genes. Finally we will aim at understanding how these populations react when facing an immune challenge, and how they are maintained and evolve during aging.

Cell-type specific and temporal regulation of transgene expression in primary cell culture of drosophila neurons

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TAR DNA-binding protein-43 (TDP-43) and Fused in Sarcoma (FUS) have recently been identified as major components of intraneuronal and intraglial inclusions in several patients with amyotrophic lateral sclerosis (ALS) or frontotemporal lobar dementia with ubiquitin positive inclusions (FTLD-U). These ubiquitary proteins are involved in numerous stages of RNA metabolism since transcription to mRNA translation. Identification of mutations in genes encoding TDP-43 and FUS in ALS patients underlines the causal role of these proteins in neurodegenerative processes. Despite numerous studies, the associated pathological mechanisms are not yet well understood.

To decipher the molecular and cellular mechanisms underlying TDP-43 and FUS neurotoxicity, several transgenic drosophila models expressing these human proteins have been generated and characterized in our laboratory. When overexpressed in adult brains, these proteins present pathological biochemical characteristics and induce neurodegeneration without massive cell loss. Due to the complexity of neural network, the study of these disease mechanisms through the whole brain remains difficult. To overcome these difficulties, an alternative approach lies in the usefulness of primary neuronal cultures. However, this tool remains undeveloped in Drosophila.

Through collaboration with Zolt Lenkei's team (ESPCI), we brought in our laboratory a newly developed and unpublished protocol of primary neuronal cultures from drosophila larval brains. We undertook the characterization of several neural parameters: cell morphology, cell polarity, neurons/glia ratio, synaptic machinery. Moreover, to limit the neurodevelopmental effects associated with the overexpression of toxic proteins from embryogenesis, we adapted the inducible GAL4 GeneSwitch system and the repressible QF/QUAS system to this new protocol. They allowed us to regulate in a cell-type specific manner (neurons, glial cells, subpopulations) the expression of a transgene during or after differentiation of neurons in vitro.

With this new adjustable system, we will now investigate the neurotoxicity of TDP-43 and FUS at the cellular stage in Drosophila.

Real-time analysis of the endosomal trafficking of Drosophila Notch and Sanpodo using a dual GFP/Cherry tagging approach

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Signaling and endocytosis are highly integrated processes that regulate cell fate. In the Drosophila sensory bristle lineages, Numb inhibits the recycling of Notch and its trafficking partner Sanpodo (Spdo) to regulate cell fate following asymmetric cell division. Here, we have used a dual GFP/Cherry tagging approach to study the distribution and endosomal sorting of Notch and Spdo in living pupae. The specific properties of GFP, i.e. quenching at low pH, and Cherry, i.e. slow maturation time, revealed distinct pools of Notch and Spdo: cargoes exhibiting high GFP/low Cherry fluorescence intensities localized mostly at the plasma membrane and early/sorting endosomes whereas GFP low/Cherry high cargoes accumulated in late acidic endosomes. These properties were used to show that Spdo is sorted towards late endosomes in a Numb-dependent manner. This dual tagging approach should be generally applicable to study the trafficking dynamics of membrane proteins in living cells and tissues.

New genes and mechanisms establishing Left-Right Asymmetry

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Left/Right (LR) asymmetry in organ shape and positioning is a common feature among species but little is known about the morphogenetic mechanisms underlying stereotyped organogenesis. In the laboratory we use two different asymmetric organs to study LR asymmetric development: the 360° clockwise rotation (Dextral) of the drosophila male genitalia, and the adult hindgut Dextral looping. The discovery of mechanisms involved in breaking the initial symmetry remains an important challenge in developmental biology. We previously described the non-muscular Myosin ID (MyoID) as the Dextral factor, the null MyoID mutation leading to a total inversion of the LR axis (sinistral development). We recently show that MyoID acts in both tissues independently and we identified the Planar Cell Polarity pathway as a major actor of adult Hindgut asymmetric looping. We also characterized the HOX gene Abdominal-B (Abd-B) as the master-gene controlling the expression of MyoID as well as the expression of recessive sinistral pathway actors. The downregulation of Abd-B leads to a naive symmetric phenotype indicating that Abd-B controls the transition from symmetry to asymmetry. In this poster, we summarized our finding and present the strategies developed in the lab in order to characterize new players required in the early asymmetric determination and propagation. We proposed to identify the role of newly identified MyoID partners and, through different approaches (ChIP-seq, TRAP, Dam-ID), to identify new Abd-B target genes involved in Sinistral and Dextral development.

Symmetry breaking by Planar Cell Polarity, Crumbs down-regulation and junction remodelling direct asymmetric cell division in a Drosophila epithelium

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Sensory Organ Precursor cells (SOPs) divide asymmetrically within the plane of the epithelium in Drosophila. Asymmetry at mitosis critically depends on the polarized distribution of the PAR polarity complex. When and how this complex localizes asymmetrically is not known. Here, we show that Bazooka (Baz), Par6 and atypical Protein Kinase C (aPKC) become planar polarized prior to mitosis and identify Planar Cell Polarity (PCP) as the initial symmetry breaking input. The apical protein Crumbs antagonizes the planar polarization of the Baz-Par6-aPKC complex in SOPs. Expression profiling of SOP allowed us to link a cell-specific transcriptional program to planar polarization. Specifically, Expanded (Ex) and p120/catenin (p120ctn) were expressed at lower levels in SOPs, inhibited the planar polarization of SOPs and regulated Crumbs and AJ dynamics. We propose a model whereby low levels of Ex and p120ctn in SOPs promote the formation and polarization of the Baz-Par6-aPKC complex. Thus, our study links fate determination to asymmetric cell division and provides a general framework to understand how epithelial cells can divide asymmetrically despite having junctions.

Role of the E3 ubiquitin ligase in the regulation of mesoderm invagination in drosophila Melanogaster:

Gantas PEREZ-MOCKUS and Francois SCHWEISGUTH

Gastrulation is the process that transforms a single layered embryo into a three layered organism. It is characterized by a series of cell movements that cause the invagination of the mesoderm. These morphogenetic movement have been extensively studied, however not everything is understood.
The Bearded (Brd) family of genes are a small family of genes that have the only known function of inhibiting the E3 ubiquitin ligase Neuralized.
During gastrulation Neuralized is exclusively active in the mesoderm. The ectopic expression of Brd in the mesoderm inhibit the activity of Neuralized and perturb mesoderm invagination. This suggested that Neuralized may have a role in regulating this process.
Here we investigate the novel role of the E3 ubiquitin ligase Neuralized in the regulation of this process. To do so we first use genetics and live and fixed imaging to study the effect of the lack of Neuralized on gastrulation.
In fixed embryos, the depletion of maternal Neuralized from the early embryos by the novel method degradFPperturbed the mesoderm invagination in a similar way than the ectopic expression of the Brd genes alloing us to conclude that Neuralized is required for this process.
We are currently trying to use live imaging using a spinning disk to unravel the mechanism perturbed in the absence of Neuralized. To do so we are looking at myosin accumulation, cell shape change and junction dynamics in different genetic contexts: in a context where Neuralized activity in the mesoderm is inhibited by the ectopic expression Brd genes, or in a context where Neuralized protein is degraded and absent in the early embryo. Snail inhibits Brd expression, and Brd inhibits Neuralized. So Snail positively regulates Neuralized activity.
The study of the function of Neuralized, will allow to shed some light into how a protein indirectly regulated by Snail can control mesoderm invagination.

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