5TH LABEX SIGNALIFE MEETING

« Cell Signaling — 2022

Nov 21-22

Le Saint Paul Hôtel
29 bd Franck Pilatte - Nice

© Estrach 2022 - Epidermal stem cells in mouse skin

INVITED SPEAKERS

Scientific Sessions
Stefano Piccolo (IFOM Inst Mol Oncology, Milan, IT)
Ype Elgersma (Dept Neuroscience, Rotterdam, NL)
Arne Weiberg (Univ Munich, LMU, Inst Genetics, DE)
Chantal Desdouets (Centre Rech. Cordeliers, Paris, FR)
Stéphan Vagner (Institut Curie, Paris FR)

Takeshi Harayama (IPMC)
Nuria Romero (ISA)
Eirini Trompouki (IRCAN)
Romain Barres (IPMC)

New Session : Innovation and Entrepreneurship
Isabelle Mus-Veteau (IPMC - YEP Program)
Patrick Collombat (IBV - DiogenX)
Elvire Gouze (Innoskel)

Free registration and abstracts

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PROGRAM OVERVIEW

5th labex SIGNALIFE meeting November 21-22, 2022, Le Saint Paul Hôtel, Nice (DAY 1)

	Monday, November 21st
12:00-13:00	**Registration**
13:00-13:15	*Welcome*
	Session I, Axis 1: Cellular Architecture of Signaling Pathways chair: Studer Michèle, iBV
13:15-14:00	*Invited Keynote Lecture:* **Stefano Piccolo**, IFOM Inst Mol Oncology, Milan, IT "Shaping the living matter through mechanosignaling"
14:00-14:30	*SIGNALIFE Keynote* : **Takeshi Harayama**, IPMC "Importance of diverse but balanced fatty acyl-chains for cellular membrane functions"
14:30-14:50	**Popkova Anna,** iBV "A genetically guided mechanical wave propagates to drive the formation of an epithelial furrow"
14:50 - 15:10	**Janardhana Kurup Akshai,** iBV "Myosin1G regulates Nodal signalling during the establishment of zebrafish Left-Right asymmetry"
15:15-15:45	**Group Picture + Coffee Break**
	Session II, Axis 2: Plasticity and Signaling chair: Bardoni Barbara, IPMC
15:45 - 16:30	*Invited Keynote Lecture:* **Ype Elgersma**, Dept Neuroscience, Rotterdam, NL "Neurodevelopmental disorders: Understanding the mechanisms and identifying treatments"
16:30 - 17:00	*SIGNALIFE Keynote :* **Nuria Romero**, ISA "Sensing the maturation timing"
17:00 - 17:20	**Tempio Alessandra,** IPMC "Characterization of the first de novo mouse model of Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)"
17:20 - 17:40	**Amiel Aldine,** IRCAN "Tissue crosstalk is required to induce a stem cell based regenerative response in the Anthozoa Cnidaria Nematostella vectensis"
	Poster Session
18:00 - 19:00	**Poster Session evaluation - Jury only (closed to the public)**
19:00 - 21:30	**Wine and Cheese Buffet and Poster Session**

5th labex SIGNALIFE meeting, November 21-22, 2022 (DAY 2)

	Tuesday November 22nd
	Session III : Innovation and Entrepreneurship chair: Braud Véronique, IPMC
09:00 - 09:20	**Isabelle Mus-Veteau**, IPMC - Labex YEP Program "Patched Therapeutics: First-in-class anticancer adjuvant for chemotherapy treatment "
09:20 - 9:40	**Patrick Collombat**, iBV - Startup DiogenX "From Bench to Valo side"
9:40 - 10:00	**Elvire Gouze**, Startup Innoskel "Development of biotherapies for skeletal dysplasia : from bench to bedside"
10:00 - 10:15	**Discussion - Round Table - on Session V**
10:15 - 10:45	**Coffee Break**
	Session IV, Axis 5: New principles in signaling and applications : Chair : Brest Patrick, IRCAN
10:45 - 11:30	*Invited Keynote Lecture:* **Stéphan Vagner**, Institut Curie, CNRS UMR3348 / INSERM U278, Paris FR "The direct contributions of RNAs to oncogenic signaling "
	Session V, Axis 3: Stress Signaling chair: Favery Bruno, ISA
11:30 - 12:15	*Invited Keynote Lecture:* **Arne Weiberg**, Univ Munich, LMU, Inst Genetics, DE "Small RNA communication between plants and pathogens"
12:15 - 12:45	*SIGNALIFE Keynote:* **Eirini Trompouki**, IRCAN "The role of repetitive elements in hematopoietic stem cell development and regeneration"
12:45-14:00	**Lunch Buffet**
14:00 - 14:20	**Lupatelli Carlotta Aurora,** ISA "Revealing principles of Phytophthora zoospores sensing and motion properties through a bio-physical approach"
14:20 - 14:40	**Mucel Inès,** C3M "p53 regulates macrophages phenotype and their capacity to handle lipids"
	Session VI, Axis 4 : Signaling in aging and disease progression chair: Gual Philippe, C3M
14:45 - 15:30	*Invited Keynote Lecture:* **Chantal Desdouets**, Centre Rech. Cordeliers, Paris, FR "Polyploidy, DNA Damage Response Driver or Gatekeeper of Chronic Liver Diseases"
15:30 - 16:00	*SIGNALIFE Keynote:* **Romain Barres,** IPMC "Epigenetic inheritance in metabolic diseases"
16:00 - 16:30	**Coffee Break**
16:30 - 16:50	**Albrengues Jean,** IRCAN "Neutrophil extracellular traps formed during chemotherapy confers treatment resistance"
16:50 - 17:10	**Carminati Alexandrine,** C3M "ROLE OF LYSYL OXIDASE LIKE 2 (LOXL2) ENZYME IN STROMAL MATRIX REMODELING AND INVASIVE PROPERTIES OF DEDIFFERENTIATED MELANOMA CELLS"
17:10 - 17:30	*Poster awards*
17:30 - 17:45	*Concluding remarks*

ORAL COMMUNICATIONS

Session I, Axis 1
Cellular Architecture of Signaling Pathways

Chair : M. Studer

Invited Keynote Lecture : Stefano Piccolo

Shaping the living matter through mechanosignaling

Stefano Piccolo

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Keywords : mechanotransduction, aging, regeneration, YAP and TAZ, stem cell

A growing body of evidence suggests that mechanical signals emanating from the cell's microenvironment are fundamental regulators of cell behaviour. Moreover, at the macroscopic scale, the influence of forces, such as the forces generated by blood flow, muscle contraction, gravity and overall tissue rigidity (for example, inside of a tumour lump), is central to our understanding of physiology and disease pathogenesis. Still, how mechanical cues are sensed and transduced at the molecular level to regulate gene expression has long remained enigmatic. The identification of the transcription factors YAP and TAZ as mechanotransducers started to fill this gap. YAP and TAZ read a broad range of mechanical cues, from shear stress to cell shape and extracellular matrix rigidity, and translate them into cell-specific transcriptional programmes. YAP and TAZ mechanotransduction is critical for driving stem cell behaviour and regeneration, and it sheds new light on the mechanisms by which aberrant cell mechanics is instrumental for the onset of ageing and of multiple diseases.

Signalife Keynote : Takeshi Harayama

Importance of diverse but balanced fatty acyl-chains for cellular membrane functions

Takeshi Harayama

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Keywords : Lipids, Metabolism, Genetics, Signaling, Cell death

Membrane lipids are essential cellular components that generate boundaries between cellular compartments, but also create an environment for membrane-associated proteins that might affect their functions. Membrane lipid structures are extremely diverse, but the relationship between lipid structures and functions remain unclear. In order to study lipid functions, it is crucial to understand the metabolic regulation of lipids. Our group combines genetic approaches, feeding of synthetic lipids, and lipidomics to analyze how lipid composition is regulated in cells. This led to the discovery of novel regulators of acyl-chains esterified in membrane glycerophospholipids. We also found that these regulators affect the sensitivity to ferroptosis, which is a cell death induced by the peroxidation of polyunsaturated lipids.

Presentation 1: Anna Popkova

A genetically guided mechanical wave propagates to drive the formation of an epithelial furrow

Anna Popkova, Matteo Rauzi

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Keywords : mechanical wave, epithelial furrowing, anterior-posterior and dorsal-ventral gene patterning systems, two-photon optogenetics, two-photon optogenetics

Epithelial furrowing is a morphogenetic process that is pivotal during embryo gastrulation, neurulation or the shaping of the animal body. A furrow often results from a fold that propagates along a line. How fold formation and propagation is initiated, driven and controlled is still poorly understood. To shed new light on this fundamental morphogenetic process, we study the formation of the cephalic furrow: a fold that runs along the dorsal-ventral axis of the embryo during early Drosophila gastrulation and which developmental role is still unknown. Here, we provide evidence of its function and show that the cephalic furrow is initiated by two groups of cells located on the left and right lateral sides of the embryo. These cellular clusters work as a pacemaker triggering a bi-directional morphogenetic wave powered by actomyosin contractions and sustained by de novo apex-to-apex cell adhesion. The position of the pacemakers is under the cross-control of the embryo anterior-posterior and dorsal-ventral gene patterning systems. Thus, cephalic furrow initiation and propagation is driven by a mechanical trigger wave that travels along a genetic guide.

Presentation 2: Akshai Janardhana Kurup

Myosin1G regulates Nodal signalling during the establishment of zebrafish Left-Right asymmetry

Akshai J. Kurup, Thomas Juan, Maximilian Furthaüer

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Keywords : Left-Right Asymmetry, Zebrafish, Nodal signalling, Myosin1G, Endocytosis

Left-Right (LR) asymmetry refers to the asymmetric placement of organs across the midline. Dysregulation of LR asymmetry establishment during development leads to multiple defects. I use zebrafish as a model to study the mechanisms that establish LR asymmetry. In zebrafish, a ciliated organ - Kupffer's Vesicle (KV) acts as a central LR organizer (LRO). The Nodal ligand Southpaw (Spaw) and its antagonist Dand5 are initially expressed in a symmetric fashion around the LRO. The beating of cilia in the LRO establishes a directional fluid flow that represses Dand5 on the left, allowing Spaw to spread on the left side through auto-induction and thereby direct the laterality of heart, brain and viscera. In contrast to vertebrates, Drosophila establishes LR asymmetry independent of cilia using chiral cell remodeling controlled by Myo1D. Our group showed previously that zebrafish Myo1D regulates LR asymmetry by orienting KV cilia and promoting the formation of a symmetry-breaking fluid flow. In addition to myo1d, the zebrafish genome encodes the closely related gene myo1g. My objective of was to study the role of Myo1G in zebrafish LR asymmetry. KV acts as a central LRO that controls the laterality of the different organs. Accordingly, myo1d mutants that have an altered LRO flow present LR defects in heart, brain and viscera. In contrast, myo1g mutants present LR defects in heart and brain but not viscera, suggesting that myo1g may exert a flow-independent function in LR asymmetry. My work reveals that in contrast to Myo1D which regulates LRO cilia orientation, Myo1G is required for the Nodal-mediated transfer of laterality information from the central LRO to different target tissues. In myo1g mutants, spaw expression remains limited to the posterior of the embryo, properly guiding the laterality establishment of the posterior viscera, whereas the anterior heart and brain fail to establish laterality. An important aspect of Nodal signaling is auto-induction, the property by which signal transduction induces its own expression. Thus, for spaw signaling, the efficient signaling in a local source furthers the production of ligand, which spreads onto the neighboring cells leading to the tissue level expression pattern. My studies based on spaw overexpression indicate that the signaling downstream of Nodal ligand binding happens inefficiently in myo1g mutants. Similarly, Overexpression of spaw along with myo1g makes downstream signaling more efficient. These results identify myo1g as a factor promoting spaw signaling activity. Previous studies implicate Myosin1 proteins in the endocytic trafficking of TGFβ receptor molecules. Different endocytic pathways have been shown to either promote TGFβ receptor signal transduction or conversely trigger receptor degradation. My work shows that myo1g mutants present a decrease in the number of Nodal-receptor positives endosomes, suggesting thereby that Myo1G may regulate LR asymmetry by controlling TGFβ recept

Session II, Axis 2
Plasticity and Signaling

Chair : B. Bardoni

Invited Keynote Lecture : Ype Elgersma

Mechanisms underlying Angelman Syndrome

Y. Elgersma

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Keywords : Neurodevelopmental disorders, Ubiquitin E3 ligase, Antisense Oligonucleotide treatment, Critical period

Angelman syndrome (AS) is a severe neurodevelopmental disorder caused by mutations affecting the maternally inherited UBE3A gene. UBE3A is a ubiquitin ligase that marks proteins for degradation. Although most studies focus on the synaptic function of UBE3A, we show that UBE3A is highly enriched in the nucleus of mouse and human neurons. Mice lacking the nuclear UBE3A isoform recapitulate the behavioral and electrophysiological phenotypes of AS mice, whereas mice harboring a targeted deletion of the cytosolic UBE3A isoform are unaffected, suggesting that the role of UBE3A is mostly nuclear [2]. In agreement with these findings, we found that many AS-associated UBE3A missense mutations affect nuclear localization of UBE3A. However, the precise role of UBE3A in the nucleus remains to be identified, which hampers the development of targeted therapeutics. A previous study has shown that the paternally inherited (imprinted) UBE3A allele can be activated using antisense oligonucleotides (ASO) [3]. However, ASO treated AS mice did show a significant phenotypic rescue, possibly because of insufficient levels of UBE3A expression or because treatment was initiated in adult mice [4]. We reinvestigated this by ASO treatment of young AS mice. We observed robust UBE3A reinstatement in the brain, with levels up to 90% of wild-type levels in the hippocampus. In addition we observed a significant improvement of several previously established AS phenotypes such as sensitivity to audiogenic seizures, open field and forced swim test, motor coordination and hippocampal plasticity. No rescue was observed for the marble-burying and nest building phenotypes. Taken together, our findings highlight the promise of ASO mediated reactivation of UBE3A as a disease modifying treatment for Angelman syndrome. 1. Avagliano Trezza RA, et al. (2019) Nat Neurosci 22:1235–1247 2. Bossuyt SNV, et al (2021) Hum Mol Genet 3. Meng L, et al (2015), Nature 518:409–412 4. Silva-Santos S et al. (2015) J Clin Invest 125:2069–2076

Signalife Keynote : Nuria Romero

Sensing the maturation timing

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Keywords : Developmental Timing - Puberty - Drosophila - Sensory organs - Neuroendocrine axis

The timing at which Juvenile-to-adult developmental transition (JDT) occurs defines the right moment to tilt the resources from growth to reproduction. JDT is a maturation process arising after the activation of the neuroendocrine axis. Therefore, complex crosstalk between growth/metabolism and the neuroendocrine axis has been established in vertebrates and invertebrates. Nevertheless, several observations support that JDT timing determination also require the integration of non-metabolic information. Emblematic examples of this include delayed maturation in isolated rats, advanced development of chickens exposed to high temperatures, and early pupation in infected female mosquitoes. Such unknown non-metabolic integration cries out for an explanation. This seminar will summarize our recent results regarding how the neuroendocrine system integrates non-metabolic environmental signals. For this, we use the Drosophila model, in which we and others have established that the neuroendocrine axis shows several structural and functional parallels even with mammals.

Presentation 1: Alessandra Tempio

Characterization of the first de novo mouse model of Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)

Tempio A. 1,2*, Delhaye S.1*, Drozd M. 1*, Duprat F.3, Capitano F.3, Weinzettl P.4, Eskenazi C.4, Jarjat M.2, Boulksibat A.1, Sirera J.5, Ciranna L.2, Gwizdek C.1, Poncer J.C.4, Mantegazza M.3, Bardoni B.3

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Keywords : KCC2, Epilepsy, first de novo mouse model, EIMFS

The potassium-chloride co-transporter KCC2, encoded by the Slc12a5 gene, is the major chloride (Cl−) extruder expressed in neurons and plays a pivotal role in controlling neuronal chloride homeostasis. In mature neurons, KCC2 maintains a low intracellular chloride concentration, such that activation of γ-aminobutyric acid type A (GABAA) receptors causes a chloride influx, resulting in membrane hyperpolarization and inhibition. KCC2 dysfunction has been associated with numerous neurological and psychiatric disorders, including epilepsy, neuropathic pain, schizophrenia and autism spectrum disorders. In particular, mutations in the Slc12a5 gene are implicated in Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), a rare and severe epilepsy syndrome characterized by multifocal seizures, developmental arrest or regression and a distinct ictal pattern on the electroencephalogram. We report the first de novo mouse model of EIMFS. These mice carry a mutation in the Slc12a5 gene (c.2569C>G; R857G). The mutation is located at the same amino acid residue found mutated (R857L) in a patient affected by EIMFS and intellectual disability. Mice heterozygous for this mutation exhibit spontaneous tonic-clonic seizures. To further characterize this model, we performed telemetric video-electrocorticographic recordings and observed the occurrence of interictal spikes in 2-month-old, heterozygous Kcc2 mutant mice. We also assessed the behavioral phenotype of these mice, which showed memory deficits in a novel object recognition task. These results suggest that our model at least partly recapitulates the human disorder. To better understand the pathophysiology, we explored the impact of the R857G mutation on KCC2 glycosylation, which has been shown to regulate KCC2 expression and function. Our data show that the mutated transporter exhibits reduced glycosylation compared to the wild-type. This effect is associated with a reduction in the membrane-inserted fraction and clustering of the transporter, which accumulates intracellularly. Finally, KCC2 has been shown to regulate neuronal actin cytoskeleton independently of its ion transport function, with consequences for neuronal maturation and synaptic function, including the dendritic spine growth. We therefore tested the impact of the R857G mutation on dendritic spine morphology and observed brain region-specific alterations in spine density and length that may impact neuronal activity. Taken together, our findings suggest that KCC2 R857G mice represent a new model of EIMFS that may serve as a platform to identify key cellular and molecular pathways that are compromised in EIMFS, thus providing an opportunity to study the etiology and pathophysiology of the disease in vivo

Presentation 2: Aldine Amiel

Tissue crosstalk is required to induce a stem cell based regenerative response in the Anthozoa Cnidaria Nematostella vectensis

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Keywords : stem cell, whole body regeneration, tissue repair, tissue crosstalk, cnidaria

Whole-body regeneration (WBR) is a key process for the survival of many species. While this process has fascinated people for centuries, little is known about the origin of the inductive signal that translates the amputation stress into a cooperative cellular response, often involving stem cells. How those specific cells capable of being initiated, synchronised and interact with the surrounding cells to build an entire functional body part during extreme regeneration remains notfully understood. To provide novel and comparative insights into these questions, we investigated the tissular and cellular dynamics underlying WBR in the emerging model cnidarian anthozoan, Nematosella vectensis. We performed a series of dissections and grafts, coupled with labelling and EdU pulse and chase experiments. Furthermore, we used spatio-temporal gene expression data as well as single cell imaging approaches to gain insight into the molecular signature and fate of activated cell populations. We identified a regeneration-inducing structure responsible, viaa tissue crosstalk, for the initiation of the repair program. We further revealed for the first time in anthozoan cnidarians, that fast and slow-cycling/quiescent, potential stem cells, respond to the amputation stress and actively participate in the reformation of lost body parts. Importantly, a synergic interaction of both stem cell populations is required to complete the regeneration process.
Our findings suggest that the emergence/loss of structure complexity/compartmentalization influences the proprieties of tissue plasticity, change the competence of a tissue to reprogram and, in the context of regeneration, the capacity of the tissue to emit or respond to a regeneration-inducing signal.

Session III, Innovation and Entrepreneurship

Chair : V. Braud

Start-up creator : Isabelle Mus-Veteau

Patched Therapeutics: First-in-class anticancer adjuvant for chemotherapy treatment

ISABELLE MUS-VETEAU & STÉPHANE AZOULAY

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Keywords : Cancer, chemotherapy resistance, drug efflux, Patched, cancer therapy

Despite advances in biomedical research and the development of new therapeutic strategies, cancer remains one of the leading causes of mortality worldwide. One of the current major challenges is the resistance of cancers to chemotherapy treatments inducing metastases and relapse of the tumor. In order to meet this medical need, we propose - An innovative and promising target: Patched. The Hedgehog receptor Patched is expressed in many aggressive cancers. We discovered that Patched transports chemotherapeutic drugs out of cancer cells, and significantly contributes to the resistance to chemotherapy of cells from different cancers such as adrenocortical carcinoma, melanoma and breast cancers. - An innovative component: Panicein A hydroquinone (PAH). We showed that PAH, a small molecule produced by a marine sponge, inhibits Patched' drug efflux activity and increases the effectiveness of chemotherapy treatment on melanoma cells in vivo without adverse effects, as well as on breast cancer cells in vitro. Our results indicate that the use of PAH as an adjuvant to chemotherapy may improve the efficacy of current chemotherapy treatments for patients with Patched expressing cancer and increase their chances of survival. Pre-maturation funding from the CNRS and SATT-SE allowed us to reach a level of maturity equivalent to TRL3. Our objective is to bring PAH or an optimized analogue to clinical phases.
Support obtained from the Young Entrepreneur Program from the Labex Signalife and the Start-up Deeptech program from Université Côte d'Azur will allow us to progress on the optimization of our compound to become a drug candidate, as well as on the in vitro and vivo proofs of concept necessary to raise the funds required to complete this project. The start-up Patched Therapeutics will complete the pre-clinical study of our lead compound, continue to develop its analogues, perform the regulatory pre-clinical and the pilot clinical phases I/II. If successful, we will negotiate the sale of the start-up to a pharmaceutical company to carry out the phase III clinical trial and bring our drug candidate to the market.

Start-up creator : Patrick Collombat

From Bench to Valo side

P. COLLOMBAT

(1) Université Côte d'Azur

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Keywords : Diabetes, startup

Type 1 diabetes is a condition that results from the autoimmune-mediated loss of pancreatic insulin-producing beta-cells. Despite current therapies (mostly insulin supplementation), diabetic patients still display an overall shortened life expectancy and a strongly altered quality of life.
Interestingly, we have recently identified a compound inducing pancreatic insulin-producing beta-cell neogenesis. Through a startup established in the laboratory, we demonstrated that this compound is efficient in vitro, ex vivo, in vivo, able to prevent the loss of insulin-producing beta-cells in mouse models of diabetes, and also capable of inducing human beta-cell genesis. The different steps/challenges leading to the creation of the startup, the work performed and the perspectives will be discussed.

Start-up creator : Elvire Gouze

Development of biotherapies for skeletal dysplasia : from bench to bedside"

Elvire Gouze

(1) InnoSkel, BioParc, 2400 Route des Colles, 06410 Biot, France

(*corresponding author : elvire.gouze@innoskel.com*)

Keywords : Innovation, rare disease, skeletal dysplasia, gene therapy, patient access

Our lead asset is INS-101, a gene therapy for type II collagen disorders, which has demonstrated strong efficacy in preclinical studies.
The most common type II collagen disorder causing disproportionate short stature is Spondyloepiphyseal Dysplasia congenita (SEDC). SEDC is present from birth and is associated with skeletal deformities that worsen with age, some of which can be life-threatening requiring repeat surgical procedures. Other complications may include respiratory insufficiency, joint pain, hip and spine deformities and early onset of osteoarthritis. INS-101 is designed to be administered systemically and restore COL2A1 function in growth plates. INS-101 has demonstrated strong efficacy in a mouse model, showing restoration of bone growth and prevention of disease complications.
We are leveraging this technology and our know how to develop other therapies to treat other serious rare bone disorders. As we progress our platform, we will be working closely with the patient community and their families. Innoskel is committed to advancing its novel therapies to provide hope for the rare bone disorder community.

Session IV, Axis 5

New principles in signaling and applications

Chair : P. Brest

Invited Keynote Lecture : Stephan Vagner

The direct contributions of RNAs to oncogenic signaling

Stephan Vagner

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Keywords : RNA, translation, MAPK, melanoma

Regulation of translation initiation plays a central role in eukaryotic gene expression and requires the action of many translation factors. Of these, the eukaryotic initiation factor 4 (eIF4F) complex, that binds to the mRNA 5'-cap, can selectively regulate the translation of mRNAs. How these activities of eIF4F are modulated in different tissue, environmental contexts and pathological conditions is an intense field of investigation. I will present efforts in my lab to unravel the specific roles of eIF4F in the resistance to anti-cancer targeted therapies and how our discoveries may be useful in the clinic.

Session V, Axis 3
Stress Signaling

Chair : B. Favery

Invited Keynote Lecture : Arne Weiberg

Small RNA communication between plants and pathogens

Arne Weiberg

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Keywords : Plant-microbe interaction, cross-kingdom RNAi

RNA communication across kingdoms has emerged as a new frontier in host-pathogen infection research. In a pioneering work, the fungal plant pathogen Botrytis cinerea was found to send small RNAs into its host plants to establish infection. These fungal small RNAs hijack the plant`s own RNA silencing machinery to suppress important plant immunity genes. That is why this virulence mechanism was termed cross-kingdom RNA interference (ckRNAi). Once this fascinating phenomenon was discovered in a fungal pathogen infection, obvious questions arose: how important is ckRNAi in nature and how are small RNAs transported from pathogens to plants? To address these questions, my lab is exploring ckRNAi in two different plant pathogen species, the fungus Botrytis cinerea and the oomycete Hyaloperonospora arabidopsidis. We have now found evidence that both species use ckRNAi to infect their host plants. In mammals, small RNAs encapsulated in extracellular vesicles (EVs) have been found to mediate cell-to-cell communication. We found first evidence for a functional role of pathogen EVs in transporting small RNAs into host plants to induce ckRNAi.

Signalife Keynote : Eirini Trompouki

Repetitive elements as signals for developmental and regenerative hematopoiesis

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Keywords : hematopoiesis, regeneration, development, stem cells, repetitive elements

Repetitive elements like transposable elements (TEs) and other simpler repeats are dispersed throughout the genome and consist more than one third of it in multiple species. For many years this part of the genome was considered as “junk”, but it has lately become clear that many functions can be attributed to repetitive elements. Developmental processes and cellular states exhibiting high plasticity are often accompanied by expression of repetitive elements. Here we show that repetitive elements are transcribed during hematopoietic stem cell development and chemotherapy-induced regeneration. Repetitive element RNAs act as signals for innate immune receptors of the RIG-I-like receptor family. Activation of these receptors titrates the induction of sterile inflammatory signals that enhance hematopoietic stem cell development and chemotherapy-induced regeneration. Thus, RNA sensing of repetitive elements actively shapes cellular transitions.

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Presentation 1: Carlotta Aurora Lupatelli

Revealing principles of Phytophthora zoospores sensing and motion properties through a bio-physical approach

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Keywords : Phytophthora zoospores, plasma membrane, sensing, motility, plant-pathogen signalling

In the soil, the epidemic spread of Phytophthora diseases is primarily based on dispersal of unicellular, bi-flagellated and polarized zoospores. Recent studies suggested that many guidance factors, e.g. soil and host-plant signals, orchestrate the early events of zoospores root colonization. However, the mechanisms underlying zoospores perception, resulting in the directed motion, remain to be elucidated. Plasma membrane proteins play a fundamental function during plant-pathogen interactions including stimuli perception by pathogens and intracellular and extracellular signalling. Lack of detailed information on the membrane protein repertoire in Phytophthora zoospores prevents a comprehensive understanding of how zoospores communicate with their environment, in particular during their pathogenic interaction with the host. The first objective of this research is to investigate the membrane protein content of Phytophthora parasitica zoospore. First, we developed a proteomic workflow based on the preparation of plasma membrane-enriched samples (zoospore, cell body, flagella), detection of peptides by LC-MS/MS approach, identification of related-proteins, mapped against P. parasitica reference proteome, and discrimination of flagella and cell body relative protein abundance using PEAKS Studio Xpro software. The second objective is now to reveal the biochemical mechanisms and physical forces governing the directed motion of P. parasitica zoospores. Pharmacological and physical approaches are developed to functionally characterise our proteomic findings and to analyse zoospores motion metrics (velocity, trajectory, cell rotation and flagellar beating frequencies) under different experimental conditions. Finally, we generated a live-cell analysis method that allows, by mimicking the rizospheric microenvironment, to specifically discriminate the effect of distinct external stimuli on zoospores sensing and motility capability in comparison with other soil microorganisms. The bio-physical approach will enable to develop a better understanding of the sensing mechanisms and motion responses governing plant-infecting zoospores.

Presentation 2: Inès Mucel

p53 regulates macrophages phenotype and their capacity to handle lipids

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Keywords : adipose tissue, macrophage, p53, obesity, insulin resistance

Metabolic reprogramming of adipose tissue macrophages (ATM) during obesity plays a major role in adipocytes dysfunction and contributes to the development of insulin resistance (IR) and Type 2 Diabetes. Transcription factors (TF) are crucial regulators of transcriptional programs involved in the polarization and adaptation of macrophages to their environment. Preliminary data showed an increase in the expression and activation of p53 in obese ATM. Thus, we decided to investigate the role of p53 in macrophages polarization, and its impact on adipocyte function. We used bone marrow-derived macrophages (BMDM) knockout (KO) for p53 and control BMDM, that we polarized into macrophages metabolically activated (MMe) with insulin, palmitate, and glucose, which phenocopy obese ATM phenotype. We showed that macrophages polarized into MMe produced inflammatory mediators and expressed lipid handling genes. The invalidation of p53 potentiate the polarization into MMe with an upregulation of genes involved in lipid metabolism such as Pparγ1, Cd36 and Abca1.
Moreover, the cellular respiration was increased in p53 KO MMe compared to control MMe, suggesting a better oxidative capacity. In contrast, the activation of p53 before the polarization into MMe decreased the respiration compared to control MMe. Strikingly, compared to conditioned-media (CM) from control MMe, CM from p53 KO MMe did not alter insulin-induced PKB phosphorylation and the expression of insulin signalling genes in adipocytes. Moreover, adipocytes treated with CM from p53 KO MMe exhibited an upregulation of genes involved in lipogenesis. In conclusion, our data suggest that activation of p53 in ATMs during obesity inhibits their ability to manage lipid and their oxidative capacity and contributes to the secretion of factors impairing insulin signalling in adipocytes. Thus, the dysregulation of p53 in macrophages during obesity could contribute to adipose tissue dysfunction and IR

Session VI, Axis 4
Signaling in aging and disease progression

Chair : P. Gual

Invited Keynote Lecture : Chantal Desdouets

"Polyploidy, DNA Damage Response Driver or Gatekeeper of Chronic Liver Diseases"

Donne R , Cordier P, Kabore C, Saroul-Ainama I, Galy-Fauroux I, Caruso S, J. Zucman-Rossi, Tran A, Couty JP, Gual P, Paradis V, Celton-Morizur S, Heikenwalder M, Revy P, Desdouets C

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Keywords : Hepatocytes, Polyploidy, Replication Stress, DNA damage, NAFLD.

Polyploidy is a fascinating characteristic of liver parenchyma. Hepatocyte polyploidy depends on the DNA content of each nucleus (nuclear ploidy) and the number of nuclei per cell (cellular ploidy). Which role can be assigned to polyploidy during human hepatocellular carcinoma (HCC) development is still an open question. Here, we investigated whether a specific ploidy spectrum is associated with clinical and molecular features of HCC. We first observed that during liver tumorigenesis, physiological polyploid hepatocytes (binuclear cells) are barely present in HCC tumors. Remarkably, mononuclear hepatocyte (nuclear ploidy) are specifically amplified in HCC tumors. In fact, nuclear ploidy is amplified in HCCs harboring a low degree of differentiation and TP53 mutations. Our results demonstrated also that mononuclear polyploid tumors are associated with a poor prognosis. We propose that related to clinical practice, quantification of cellular and nuclear ploidy spectra could be an accurate test for HCC prognosis. Our more recent study investigated the mechanisms underlying the activation of DNA damage response during NAFLD. Using murine models recapitulating human NAFLD disease, we demonstrated that steatotic hepatocytes display hallmarks of Replicative Stress (RS), including slow replication fork progression and ATR-mediated replication stress response. RS was sufficient to elicit DNA lesions. Importantly, these cells that have experienced RS display an activation of the cGAS-STING pathway. Our data shed new lights on the molecular mechanisms by which damaged NAFLD hepatocytes promote disease progression.

Signalife Keynote : Romain Barres

Epigenetic rewiring of skeletal muscle after exercise training

Barrès et al.

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Keywords : Epigenetic, Metabolism, GWAS, histones, DNA methylation

This talk will present recent work from the laboratory of Prof. Barrès which focused on the study of the epigenetic rewiring of gene enhancers after endurance training in humans and its role in the control of gene expression and the modulation of disease risk. Prof. Barrès says “We know that regular physical exercise improves health by reducing the risk of a plethora of chronic disorders, but the genomic mechanisms at play in skeletal muscle are largely unknown”. In this presentation, Prof. Barrès will detail an multiomics strategy integrating transcriptomic data, genome wide association studies and the mapping enhancers activity in skeletal muscle biopsies collected from young sedentary men before and after endurance exercise. “We identified an enrichment of disease-associated genetic variants within the exercise-remodelled enhancers” says Prof. Barrès. “Notably, some genes we have identified are candidates to regulate the beneficial effect of exercise training on human brain function”.

Presentation 1: Jean Albrengues

Neutrophil extracellular traps formed during chemotherapy confers treatment resistance

Alexandra Mousset (1), Enora Lecorgne (1), Isabelle Bourget (1) , Pascal Lopez (1), Chloé Dominici (1), Kitti Jenovai (1), Julien Cherfils-Vicini (1), Mikkel Green Terp (2), Mikala Egeblad (3), Cédric Gaggioli (1), Jean Albrengues (1)

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Keywords : Metastasis, Chemoresistance, Inflammation, Neutrophils, Signaling

Metastasis is the major cause of cancer death and although most patients with metastases are treated with chemotherapy, the development of therapy resistance is common. The tumor microenvironment can confer chemoresistance, yet little is still known about how specific host cells influence therapy outcome. We show that chemotherapy induced neutrophil recruitment and Neutrophil Extracellular Trap (NET) formation which reduced therapy response in a mouse model of breast cancer lung metastasis. We found that chemotherapy-treated cancer cells released adenosine triphosphate causing other cancer cells to secrete IL-1β, which in turn triggered neutrophils to form NETs. Two NET-associated proteins where required for NETs' ability to induce chemoresistance: first, integrin-αvβ1 in NETs trapped latent TGFβ. Then, matrix metalloproteinase 9 cleaved and activated the trapped latent TGFβ. The NET-mediated TGFβ activation caused cancer cell to undergo epithelial to mesenchymal transition and correlated with chemoresistance. Critically, pharmacologically targeting of IL-1β, NETs, integrin-αvβ1, MMP9, and TGFβ all dramatically improved chemotherapy response in our mice model. Our work establishes a novel paradigm for how NETs regulate activities of neighboring cells by trapping and activating cytokines. Additionally, our data suggest that chemotherapy resistance in the metastatic setting can be reduced or prevented by targeting the previously unrecognized IL-1β-NET-TGFβ axis

Presentation 2: Alexandrine Carminati

Role Of Lysyl Oxidase Like 2 (Loxl2) Enzyme In Stromal Matrix Remodeling And Invasive Properties Of Dedifferentiated Melanoma Cells

Alexandrine Carminati, Serena Diazzi, Pierric Biber, Margaux Lecacheur, Christophe Girard, Mehdi Khaled, Sophie Tartare-Deckert* And Marcel Dekcert*. *Equal Contribution

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Keywords : melanoma, LOXL2, ecm remodeling, phenotypic transition, targeted therapies

Cutaneous melanoma is a highly malignant and invasive skin cancer. Despite successful therapies targeting the BRAFV600E oncogenic pathway or immune checkpoints, resistances occur. Upon microenvironment and therapeutic pressures, melanoma cells can switch from a melanocytic differentiated state to dedifferentiated states associated with increased expression of receptor tyrosine kinases (RTKs) and mesenchymal markers. Such adaptive plasticity was described as a driver of resistance to targeted therapies (TT). We previously described that dedifferentiated cells can acquire extracellular matrix (ECM) remodeling activities and that tumor exposure to BRAF inhibitors (BRAFi) induces tumor stiffening. Proteomic analysis of components of the extracellular matrix (ECM) (matrisome) deposited by TT-resistant cells revealed an accumulation of the collagen-crosslinking enzyme LOXL2. LOXL2 is a member of the Lysyl-OXidase family that drives tumor stiffening and the epithelial-to-mesenchymal (EMT) process, but its role in melanoma is still unknown. We hypothesized that LOXL2 production by melanoma cells and its presence within the stroma could influence phenotypic plasticity towards a drug-resistant dedifferentiated state. We examined melanoma cells chosen according to their phenotype and showed that LOXL2 is preferentially expressed by dedifferentiated MITFlow/AXLhigh cells. LOXL2 is induced by BRAFi/MEKi combination, TGF-β, TNFα or hypoxia, cues known to remodel and aggravate the tumor niche. On the contrary, LOXL2 induction by TT is reversed by PDGFR and AKT inhibitors and by silencing the plasticity transcription factor ZEB1. Using si/shRNA and pharmacological approaches, we revealed that LOXL2 plays a role in focal adhesion formation and cell morphology and promotes melanoma cell migration. LOXL2-dependent migration required the expression of the EMT factor SLUG. Interestingly, we also show that targeting LOXL2 in melanoma-associated-fibroblasts impaired their ability to contract a collagen matrix and to assemble an organized ECM, suggesting the implication of LOXL2 in the dialogue between melanoma cells and the stromal matrix. Together, these findings provide an original link between LOXL2, ECM remodeling and melanoma cell biology. This study improves our understanding of the biochemical and biomechanical cues from the tumor microenvironment that affect melanoma cell plasticity and adaptation to anti-melanoma therapies

POSTERS

Wine and Cheese Poster Session

LIST OF 25 POSTERS PRESENTATIONS				
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1	Andreoni-Pham	Rita	Axis 2 – Plasticity and Signaling	Regeneration is a regeneration-specific process for Nematostella vectensis
2	Bahri	Alia	Axis 3 – Stress Signaling	Environmental stress control RNA granule formation and content in C.elegans
3	Bonche	Raphaël	Axis 2 – Plasticity and Signaling	Senses like teen spirit: juvenile-to-adult transition timing controlled by environmental cues
4	Boulksibat	Asma	Axis 2 – Plasticity and Signaling	Preclinical research on a new potential therapeutic molecule to treat Fragile X Syndrome
5	Burckard	Odile	Axis 5 – New principles in signaling and applications	Coupling and synchronization of peripheral circadian clocks
6	Roby	Nicolas	Axis 1 – Cellular architecture of signaling pathways	Deciphering cell force distribution: nuclei and microtubules at play to promote composite morphogenesis
7	Clot	Charlène	Axis 4 – Signaling in aging and disease progression	Sex-specific tumor formation in the gut
8	Nicolini	Victoria	Axis 1 – Cellular architecture of signaling pathways	Glucocorticoid receptor negatively regulates Processing-bodies formation
9	Péré	Marielle	Axis 5 – New principles in signaling and applications	Integrating machine learning methods to single cell signaling analyses increases throughput and accuracy for target identification in immuno-oncology
10	Hamidouche	Tynhinane	Axis 4 – Signaling in aging and disease progression	To understand the mechanisms underlying the functions of telomerase on kidney epithelium
11	Hérault	Chloé	Axis 1 – Cellular architecture of signaling pathways	Intrinsic sexual identity controls organ size via cell cycle regulation
12	Janona	Marion	Axis 3 – Stress Signaling	Inhibition of Inositol-Requiring Enzyme 1 Alpha (IRE1α) signaling sensitives Hepatocellular Carcinoma to Sorafenib
13	Kovachka	Sandra	Axis 4 – Signaling in aging and disease progression	Inhibition of Patched1 as promising strategy to overcome chemotherapy resistance in cancer cells
14	Gaspar Litholdo Junior	Celso	Axis 3 – Stress Signaling	Plant cell wall integrity mechanisms and oomycete susceptibility
15	Ouertani	Amira	Axis 2 – Plasticity and Signaling	Deciphering the Molecular Grammar of Condensate Assembly
16	Goodluck	Benjamin	Axis 3 – Stress Signaling	Nitrogen-Fixing Bacteria Induce Defense Priming Against Pea Aphid In Medicago Truncatula
17	Rête	Tifenn	Axis 1 – Cellular architecture of signaling pathways	RNA granule remodeling in C. elegans germinal tumor
18	Casado	Doïna	Axis 2 – Plasticity and Signaling	EXPLORATORY STUDY OF SENSORY PERCEPTION OF GRAVITY in Drosophila melanogaster
19	Simonti	Martina	Axis 2 – Plasticity and Signaling	A novel mechanism of non-syndromic Autism Spectrum Disorder caused by mutations of the SCN2A gene: functional studies and knock-in mouse model
20	Tanari	Abdul Basith	Axis 1 – Cellular architecture of signaling pathways	Tuning cytoskeletal and mechanical polarity from the cell to the embryo scale to trigger gastrulation movements
21	Teisseire	Manon	Axis 3 – Stress Signaling	Targeting CTGF : A new therapeutic strategy in metastatic renal cell carcinoma ?
22	Tleiss	Fatima	Axis 1 – Cellular architecture of signaling pathways	A TrpA1/DH31-dependent closure of a pylorus-like structure is required for the IMD pathway to kill pathogenic bacteria
23	Valero	Florian	Axis 2 – Plasticity and Signaling	RNA RNA interaction and condensate assembly
24	Weerasinghe-Arachchige	Lahiru-Chamara	Axis 2 – Plasticity and Signaling	Greb1l plays a vital role during the epiblast maturation of mouse embryos.
25	Chafik	Abderrahman	Axis 3 – Stress Signaling	Control of mitochondrial functions by endosomal GTPase Rab4b-dependent mechanisms

1 - Andreoni-Pham Rita – Axis 2

Regeneration is a regeneration-specific process for Nematostella vectensis

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Keywords : Nematostella vectensis, sea anemone, Regeneration, Apoptosis, Tissue crosstalk

Regeneration is the ability to repair tissues, organs, or even whole bodies after injury. To gain novel insight into the molecular and cellular mechanisms underlying whole-body regeneration (WBR), a recent study compared embryonic development and regeneration in the sea anemone, Nematostella vectensis, suggesting that apoptosis is a regeneration-specific process required to initiate regeneration via a tissue crosstalk. However, the precise roles and their chronology during regeneration in Nematostella are yet to be determined.
We performed a detailed characterization of the tissular crosstalk responsible for the initiation of regeneration and in silico identification of pro and anti- apoptotic genes was performed as well as their spatio-temporal expression analyzed. To gain functional insight into the role of apoptosis during embryonic development and regeneration, we used the pharmacological pan-caspase inhibitor Z-VAD and assessed the resulting phenotype using tissular, molecular and cellular markers. This work revealed the precise tissular dynamics during the wound-healing process that leads to the tissue crosstalk at the origin of the regeneration process. Inhibition of apoptosis not only prevents this crucial tissue crosstalk, but also all subsequent events such as cell proliferation and the reformation of lost body parts. Our data further suggest that apoptosis and MEK/ERK signaling are both activated shortly after injury and act in parallel to coordinate the regenerative response. This work highlights the regeneration-specific role of apoptosis in Nematostella and paves the way to a detailed analysis of the molecular signals, including the apoptosis-dependent ones, underlying the regeneration-inducing tissue crosstalk.

2 - Bahri Alia – Axis 3

Environmental stress control RNA granule formation and content in C.elegans

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Keywords : Stress, RNA, granule, C elegans, translation

Gene expression must be adapted to environmental variations. Upon the massive translation repression triggered by environmental stress, translation repressors can bind mRNA transcripts and co-assemble into a condensate form: the RNA granule. Our hypothesis is that granule identity should be different according to the environmental challenges the organism is facing. In the C.elegans germline, stress conditions can trigger the assembly of aggregates that can reach the size of a nucleus (up to 10µM). We first assessed the aggregation of CAR1/LSM14/Tral, a repressor protein that can co-assemble into RNA granules. Different stresses were applied to the nematodes: sperm depletion (resulting in oogenesis arrest), ethanol shock and sudden temperature variations (heat shock and cold shock). Each stress resulted in a different RNA granule morphology. Moreover, using a smFISH (single molecule FISH), we showed that the mRNA composition in the granule is different from one environmental stress to another. Therefore, we conclude that both RNA granule formation and content depend on environmental stress, reinforcing the idea of a specific granule identity. Previous studies shown that stress granules are temporary and dissolves shortly after stress recovery. Although it has been confirmed by our results, prolonged stress however results into irreversible granules. This change in dissolution time cannot be explained by granule size, which quickly reaches a plateau after the stress. A possible explanation for the increase of granule stability is the change in granule composition over time. Another important aspect of RNA granule formation is RNA regulation. During oocyte development, maternal mRNAs that are translationally repressed in oocytes, such as spn-4, localizes to physiological RNA granules. We showed that over oocyte maturation, spn-4 is released from RNA aggregates and becomes translated. Upon heat shock, spn-4 aggregation increases and the translation is repressed. On the opposite, after a cold shock, spn-4 is released from the granule and translation increases. Therefore, granule formation is correlated to translation level and their content can vary according to the environment. In conclusion, stress RNA granules are diverse and can coordinate translation to the environmental changes.

3 - Bonche Raphaël – Axis 2

Senses like teen spirit: juvenile-to-adult transition timing controlled by environmental cues

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Keywords : Environment perception, Sensory neurons, Neuroendocrine axis, Juvenile-to-adult transition, Drosophila model

What triggers juvenile to adult developmental transition (JDT) is a biological question that concerns all sexually reproductive organisms. Researchers have made great progress establishing complex crosstalk between metabolism and the neuroendocrine axis timing JDT in vertebrates and invertebrates. However, several observations such as precocious puberty in girls exposed to chronic social stress, delayed sexual maturity observed in male orangutans exposed to a dominant male or in isolated rats, early JDT of chicken exposed to high temperatures, and precocious pupation in infected female mosquito's larvae, support the neuroendocrine integration of a plethora of non-metabolic environmental cues. Nevertheless, the mechanism underlying the non-metabolic effects on timing JDT is unknown. The sensory organs rapidly sense and distinguish many environmental cues, questioning whether the sensory system provides environmental information to the neuroendocrine axis. Therefore, we challenge the classical endocrinal view beyond hormones and metabolism by proposing a role for the sensory system in timing JDT. Interestingly, a recent reconstruction of the almost complete connectome of the Drosophila larva sensory system revealed that the neuroendocrine system receives indirect afferent inputs from different sensory neurons. Therefore, using Drosophila genetic tools, which allow neuronal activity manipulation, we performed a non-quantitative functional screen to identify a set of chemo- and mechano-sensory neurons provoking JDT timing modification, precocious or delayed. We identified 77 candidates represented primarily by chemosensory neurons. We are currently measuring the JDT timing modification for each candidate. In addition, we are also evaluating the final size that each candidate reaches for its metamorphosis in order to distinguish those with a metabolic alteration from those without. Moreover, by taking advantage of the most recent advances in a matter of transsynaptic tracing tools, we are disclosing the circuitry connecting the known neuroendocrine circuitry -AstA-Corazonin-PTTH- with the integration centers of sensory inputs in the central brain (e.g. the Antennal Lobe for the odors). In parallel, we undertook the identification of the specific environmental inputs able to time development. Focusing our efforts on the odorant cues first, we are currently testing the effect of odors and pheromones previously described as relevant for the insect behaviors, on the JDT timing. Here, we want to share the latest advances of our scientific journey to uncover the neuronal pathway integrating the non-metabolic environmental stimuli by the neuroendocrine axis

4 - Boulksibat Asma – Axis 2

Preclinical research on a new potential therapeutic molecule to treat Fragile X Syndrome

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Keywords : Fragile X syndrome - Screenings - Treatment - Small molecules - Behavior

Fragile X Syndrome (FXS) is the most common form of inherited intellectual deficiency (ID) with a prevalence of 1:4000 for men and 1:8000 for women. This syndrome is a neurodevelopmental disease, and the first symptoms are observed in early childhood. Indeed, FXS children may have a delay in speaking, be hyperactive or have motor problems. All adult patients display ID and some criteria of Autism Spectrum Disorder (ASD). No effective treatments are available for FXS. This syndrome is caused by a CGG triplet repetitions in the 5'UTR region of the Fragile X Mental Retardation 1 (FMR1) gene located on Xq27.3. The hypermethylation of the CGG-containing region and of the FMR1 promotor leads to the silencing of gene expression. FMR1 encodes the Fragile X Mental Retardation Protein (FMRP), an RNA binding protein involved in the metabolism of its mRNA targets. Indeed, FMRP can regulate the translation and transport of mRNAs coding a large subset of synaptic proteins. In vivo and in vitro models have been generated to study this pathology. The main in vivo models are Drosophila, zebrafish, rat and mouse. The most widely used FXS model is the Fmr1-KO mouse recapitulating the disease. This mutant mouse displays socio-cognitive deficits similar to FXS patients. In addition, the neuronal morphology of the Fmr1-KO neuron is altered. In our laboratory an in vitro model was generated to study FXS. Indeed, a stable knockdown of FMRP was obtained by using a specific shRNA directed against the mRNA encoding Fmr1 in mouse Embryonic Stem Cells (ESCs), generating the shFmr1 ES cells. After inducing the neuronal differentiation of these progenitors, it has been observed that the morphology of these cells is altered. This cell model has been used in collaboration with Dr Villa (Plateforme de Chimie Biologique Intégrative de Strasbourg, Strasbourg, France) to screen four libraries (Prestwick and other libraries of small molecules from Institut de Chimie de Nice, Nice, France) in order to identify those that are able to rescue the abnormal phenotype of shFmr1 ES cells. We selected four molecules with this ability, which represent new potential drugs for FXS: Small Molecule (SM) 1, SM2, SM3 and SM4. The most promising one was SM4. To assess whether SM4 treatment could repair the altered Fmr1-KO neuron morphology, we tested it on another in vitro model, Fmr1-KO primary cortical neurons and found that it could rescue the shorten length of Fmr1-KO first neurite. We also carried out in vivo studies on two models: dfmr1 flies and Fmr1-KO mice. The Drosophila study allowed us to find that SM4 is able to rescue the increased sensitivity to starvation associated to dfmr1 flies. The acute treatment of Fmr1-KO mouse, showed that SM4 could rescue their socio-cognitive deficits at different ages. Further studies on this molecule may lead to an FXS therapy.

5 - Burckard Odile – Axis 5

Coupling and synchronization of peripheral circadian clocks

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Keywords : peripheral circadian clock, synchonization, piecewise linear systems, coupling, modelling

In mammalians, every cell contains its own circadian clock, a mechanism that controls and synchronizes many cellular and molecular processes (such as heart beat, blood pressure, body temperature,...) with the Earth's light/dark cycle. In humans, environmental and genetic disruptions (jet lag, shift work, malnutrition,...) of the circadian clock are a risk factor for cardio-metabolic, inflammatory and malignant diseases. Reciprocally, diseases perturb the circadian coordination thus potentially leading to a vicious cycle. Understanding the mechanisms of synchronization of circadian clocks is therefore a question of primary importance to later implement preventive or therapeutic strategies aiming at reinforcing circadian rhythms. However, the intercellular interactions between peripheral circadian clocks, located in tissues and organs other than the suprachiasmatic nuclei of the hypothalamus (where the central clock is), are still very poorly understood. To analyze the coupling between two peripheral clocks, we used a calibrated and reduced model of the circadian clock, which recovers important properties as the oscillations of the main proteins over time or the phase opposition between BMAL1 and PER:CRY. Based on this model, we developed a piecewise linear model including two new parameters, to represent both populations of cells with different periods and the intercellular clock coupling through the complex PER:CRY, and we suggested a segmentation of the circadian clock in 6 stages, each representing one part of the circadian day. Our results show that the difference between periods of the two cells and the strength of coupling are important factors for synchronization. Interestingly, they also highlight the fact that two coupled oscillators may be synchronized in period but have different duration for each stage

6 - Roby Nicolas – Axis 1

Deciphering cell force distribution: nuclei and microtubules at play to promote composite morphogenesis

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Keywords : Morphogenesis, Cytoskeleton, Nucleus, Subcellular, In vivo

Morphogenesis is the process via which an organism acquires its shape. Tissue morphogenesis relies on forces that are generated at the cell scale via localized actomyosin contractility. While much is known of how actomyosin activity can lead to specific cell shape changes, the mechanisms underlying the precise sub-cellular localization of actomyosin contractile networks remains elusive. We use the Drosophila embryo as a model system and focus on the process of mesoderm invagination: a morphogenetic event that results in the coordinated internalization of hundreds of cells within 20 minutes, initiating embryo gastrulation. In our lab we have identified a two-tier junctional system in mesoderm cells formed by actomyosin advective networks tethered to E-cadherin: the first tier is located at the cell apical side mediating apical constriction, while the second tier is located at the cell lateral side mediating cell intercalation. These concomitant cell shape and topology changes drive a composite morphogenetic process resulting from the folding and the convergence-extension of the prospective mesoderm forming an elongating tubular epithelium. With this project we aim to unravel the origin of two-tier adherens junctions. Our data support the idea that nuclear repositioning together with microtubule architecture remodeling is responsible for two-tier junction formation. By using advanced confocal and light-sheet imaging, coupled with optogenetic control of microtubules dynamics and femtosecond infra-red laser ablation, our work will shed new light on the mechanisms controlling the sub-cellular distribution of forces responsible for composite morphogenesis

7 - Clot Charlène – Axis 4

Sex-specific tumor formation in the gut

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Keywords : sex, intestinal tumors, somatic stem cells, drosophila, neuropeptide

Disparities in cancer incidence and mortality exist according to gender. But the impact of sex on tumor formation is not well understood. To identify the molecular factors and cellular processes involved in sex-specific tumor formation, we study female-specific intestinal tumors in drosophila, by inactivating Notch in intestinal stem cells in adults. The formation of these tumors relies on the presence of transformer (tra), the female sex determinant. Our project aims to understand how these sex-specific tumors are formed. We already find out that it is possible to generate these genetically induced tumors in males, by totally feminizing them through ubiquitous expression of the female form of tra (traF). In addition, focusing on the cell type participating in tumor formation, we discovered that feminizing only some enteric neurons expressing fruP1, that corresponds to approximately 2% of the adult neurons, is sufficient to induce tumors in male guts, in same proportions as in females. Besides, these tumors always follow the same scheme when they appear: their formation is triggered in the posterior part of the midgut and propagate to the anterior region. To go further, our plan is to determine whether it is a developmental process or can it be initiated at adult stage? Also, we seek to identify the FruP1 neuronal subpopulations involved in tumor formation and the molecular players required for the communication between the FruP1 neurons and the intestinal stem cells.

8 - Nicolini Victoria – Axis 1

Glucocorticoid receptor negatively regulates Processing-bodies formation

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Keywords : Processing-bodies (Pbodies), Glucocorticoid Receptor (GR), Glucocorticoid, RNA metabolism, Liquid-Liquid Phase Separation (LLPS)

Processing-bodies (Pbodies) are described as small cytoplasmic membraneless organelles that play an important role in various cellular processes by controlling RNA translation. Pbodies are formed by the interaction of untranslated mRNA and multiple RNA binding proteins assembled by liquid-liquid phase separation (LLPS).
However, despite recent discoveries about their own key components, the cellular pathways that control their formation or dissolution are poorly understood. In this context, we have conducted an extensive drug screening to identify targets able to enhance Pbody formation. In collaboration with the PCBIS facility, we uncover that glucocorticoids were able to increase the number of P-bodies in cells after 48 hours. By combining microscopy and biochemistry experiments, we surprisingly found that this increased number of PBodies was associated with the decreased expression of the glucocorticoid receptor (GR) in response to its ligand in a dose-dependent manner. Consistent with this finding, we also showed that siGR led to an increase in the number of PBodies, demonstrating that the formation of PBodies is independent of GR induced transcription. Based on these results, we hypothesized that the cytoplasmic location of GR has a negative effect on the number of Pbodies. Namely, when GR is activated, it is translocated to the nucleus, and when we use siRNA against GR, there is less GR in the cytoplasm, where the Pbodies are located. It is now important to validate this hypothesis to better understand the relationship between the decrease in protein content of GR and the increase in the number of Pbodies in the cells. Overall, our results illustrate a non-canonical function of GR, which regulates RNA translation through a cytoplasmic LLPS.

Integrating machine learning methods to single cell signaling analyses increases throughput and accuracy for target identification in immuno-oncology

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Keywords : Single-cell, Machine-learning models, Cancer, Pharmacodynamics, Therapeutic targets

Cell response heterogeneity upon treatment is a main obstacle in preclinical development of efficacious cancer drugs, due to the emergence of drug-tolerant cells. We have previously developed a single-cell workflow, Fate-Seq (2), to profile drug-tolerant persisters, based on predictions of their drug response. To achieve this goal, Fate-Seq couples 3 single-cell techniques (1): first the prediction of the cell response phenotype (resistant or sensitive) for clonal cancer cells treated with a chosen drug, then the separation of the predicted resistant cells from the predicted sensitive ones and finally the RNA sequencing of the cells. These scRNAseq data are analyzed using random walks to prioritize the genes according to the drug-sensitive state of each cell to determine the protagonist genes responsible for cell drug-resistance (4).
To automatize and increase the prediction throughput, we present 3 major improvements in our workflow using machine learning models to classify cell drug response, from cell signaling observed with fate-seq, and determine the molecular factors of non-genetic resistance to a drug. These molecular factors represent good candidates to be targeted during a co-treatment, in combination with the first drug analyzed with our pipeline.
First, we present how we combine image processes and machine learning classification models to automatically track cells overtime and detects important cellular events like division or death. The output of this first technique are short and sparse fluorescent time-trajectories, that represent the cell signaling activity in response to the drug, with a unique signal for each cell.
We then introduce our eDRUGs (early Drug Response UpGraded) classifier, that combines mechanistic modeling of apoptosis (cell death) through cell signaling pathway, and machine learning classification models to predict cell drug response, within an hour, for a maximum number of cells, using the fluorescent time-trajectories as input. This new method is twice as accurate as our previous prediction method (3).
Finally, we will also propose a novel analysis method of sc-RNA-seq data obtained with Fate-Seq. This method consists in training binary classifiers on the scRNAseq expression data obtained from the pipeline, using a range of models and explainable AI techniques such as DeepLift (5), in addition to clustering techniques, to obtain attribution scores for each gene. These scores are expected to reveal a reduced gene set, possibly containing only tens of genes, that are predictive of drug resistance.

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10 - Hamidouche Tynhinane – Axis 4

To understand the mechanisms underlying the functions of telomerase on kidney epithelium

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Keywords: telomerase, regeneration, podocytes, Kidney, mouse genetics

Homeostatic renal filtration relies on the integrity of podocytes, which function in glomerular filtration. These highly specialized cells are damaged in 90% of chronic kidney disease, representing the leading cause of end-stage renal failure. While podocytes are thought to have a severely limited capacity for renewal in homeostatic conditions, recent studies highlighted modest podocyte renewal in adult mice following injury. Nonetheless, the mechanisms regulating podocyte renewal following injury in the adult organism remain largely unknown and controversial. Using a mouse model of Adriamycin-induced nephropathy, we report that proper recovery of filtration function following podocyte injury in wild-type mice requires up-regulation of the endogenous telomerase TERT. Previous work has shown that transient overexpression of catalytically inactive TERT (i TERTci mouse model) has an unexpected role in triggering dramatic podocyte proliferation and renewal. We therefore used this model to conduct specific and stochastic lineage tracing strategies. These experiments provide evidence that telomerase pulse drives the activation and clonal expansion of podocyte progenitor cells . Furthermore, high throughput sequencing approaches unveil the core pathways involved in TERT pro-regenerative functions in the adult kidney that includ promotion of key pathways such as extracellular matrix remodeling, inflammation, Epithelial-to-Mesenchymal transition, and KRAS . Our results further revealed activation of additional signaling pathways including Hedgehog, Wnt, and Notch in a context of TERTci-enforced regeneration. Our findings demonstrate that the adult kidney bears intrinsic regenerative capabilities involving the protein component of telomerase, paving the way for innovative research toward the development of chronic kidney disease therapeutics.

11 - Hérault Chloé – Axis 1

Intrinsic sexual identity controls organ size via cell cycle regulation

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Keywords : sex differences, size, cell cycle, cell size, drosophila melanogaster

Sex differences in body size are widespread throughout the animal kingdom but their underlying mechanisms are not well characterized. Here, we use tissue-specific genetics to investigate how sexual dimorphism in size is established in Drosophila. We find that the larger body size characteristic of Drosophila females is controlled by the female sex determinant TransformerF (TraF). We demonstrate that TraF is essential and sufficient to drive 40% of sexual dimorphism in size, independently of its two known targets: doublesex (dsx) and fruitless (fru). We find that the female-specific body size is established very early in larval stages 2 and 3 and that TraF acts cell-autonomously in every organ. In addition, we show that apoptosis and cell size are not involved in sex-specific growth, instead, TraF controls cell number by boosting proliferation in females. We now would like to identify the direct targets of TraF impacting the cell cycle. Our data suggest a model of sex-specific growth in which body size is regulated by a previously unrecognized branch of the sex determination pathway and identify TraF as a novel link between sex and cell cycle regulation.

12 - Janona Marion – Axis 3

Inhibition of Inositol-Requiring Enzyme 1 Alpha (IRE1α) signaling sensitives Hepatocellular Carcinoma to Sorafenib

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Keywords : HCC, IRE1, UPR, liver cancer, sorafenib

Introduction: HCC, the 5th most common cancer, represents the 3rd cause of leading death by cancer worldwide. One of the two current treatments, Sorafenib, has a modest effect on patient survival. The identification of new therapeutic targets is therefore urgent. The unfolded protein response (UPR) has been described as a key actor in liver pathologies, in particular IRE1α, the most conserved UPR protein, in NASH. We therefore speculated that IRE1α may also be crucial in the pathophysiology of HCC and that targeting IRE1α may be effective in treating HCC. Methods and Material: We analyzed the UPR pathway and its dialogue with the inflammasome in adjacent tumor and non-tumor tissues of a cohort of 10 patients with HCC of alcoholic origin. In combination with Sorafenib, we were able to specifically target the RNase activity of IRE1α thanks to 3 pharmacological compounds (STF/MKC/4μ8C) within 3 human lines of HCC (HepG2, Hep3B, HuH7) and 2 pre-clinical models HCC (HepG2 xenografts in immunodeficient mice and immunocompetent C57BL6 mice injected with DEN). Biochemical, gene and histological analyzes were carried out. Results: First, tumor tissues from HCC patients exhibit higher RNase activity of IRE1α and inflammasome activity compared to adjacent non-tumor tissues. We also confirmed in vitro that the RNase activity of IRE1 and the inflammasome are overactivated in HCC lines compared to primary human hepatocytes. Pharmacological and gene targeting of IRE1α allows loss of tumor viability (in vitro and in vivo) accompanied by induction of apoptosis and arrest of cell proliferation. This loss of tumor viability seems to be induced by an anti-tumor UPR response dependent on IRE1, PERK and JNK kinases. In vivo, one of our pharmacological compounds, MKC, shows robust anti-cancer efficacy in the pre-clinical model of HCC injected with DEN. We observed a significant decrease in tumor volume and systemic inflammation, accompanied by an improvement in hepatic homeostasis. Interestingly, after treatment, the non-tumor tissue adjacent to the tumors appears similar to the liver of a healthy control mouse, which may reveal a low toxicity of our compound and a targeted efficacy on the tumor areas. In addition, one of the side effects of sorafenib, weight loss, seems to be limited by the administration of MKC. Conclusion: Inhibiting the RNase activity of IRE1α improves the efficacy of sorafenib by increasing apoptosis and stopping the proliferation of cancer cells in vitro and in vivo. Interestingly, the addition of an inhibitor of RNase activity of IRE1 attenuates the side effects of Sorafenib, giving full meaning to the study of this combination in clinical trials.

13 - Kovachka Sandra – Axis 4

Inhibition of Patched1 as promising strategy to overcome chemotherapy resistance in cancer cells

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Keywords : Cancer, Multidrug Resistance, Patched1, Drug Efflux, Efflux Inhibition

Chemotherapy resistance is one of the major challenges in cancer treatment. The development of inhibitors of biological mechanisms involved in multidrug resistance (MDR) meets an important medical need but still represents a challenging task. Major MDR targets are multidrug efflux systems, such as the ATP Binding Cassette (ABC) transporters. However, their inhibition leads to severe side effects mainly related to the ubiquitous localization of these transporters thus none of the inhibitors has been approved for clinical use [1]. Therefore, alternative therapeutic targets are urgently needed.

The Hedgehog receptor Patched1 (Ptch1), part of the Hedgehog signaling pathway involved in tissue development in embryogenesis and tissue homeostasis in adults, was recently shown to transport different chemotherapeutics out of cancer cells contributing significantly to MDR phenomena in cancer treatment. Ptch1 is known to be over-expressed in many types of cancers and due to the peculiarity of its pH dependent efflux mechanism (Warburg effect), its inhibition was shown as a successful strategy in improving chemotherapy efficacy without toxicity for healthy cells or potential side-effects. To date, only few compounds have been identified as efficient Ptch1 inhibitors, among which panicein A hydroquinone (PAH), a meroterpenoid natural compound extracted from marine sponge[2].

Here we describe the first stereoselective synthesis for the E and Z isomers of PAH and we apply the methodology to several analogs with the aim of assessing a structure-activity relationship. The biological activity of the derivatives, in combination with chemotherapy, was evaluated in melanoma cells. Molecular insights into the mechanism by which the compounds bind to Ptch1 and inhibit chemotherapeutics transport are also addressed by means of in silico methodologies [3]. Altogether, these data pave the way for the design and development of the next generation of Ptch1 inhibitors.

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14 - Gaspar Litholdo Junior Celso – Axis 3

Plant cell wall integrity mechanisms and oomycete susceptibility

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Keywords : Plant cell wall integrity, oomycete, Marchantia polymorpha, Phytophtora palmivora, Feronia

Growing plant cells tightly coordinate the loosening and turgor pressure-driven deformation of their pre-existing cell wall (CW) with the precise delivery of new constituent material for membrane and CW formation. To achieve such a remarkable temporal and spatial coordination, plant cells have developed CW integrity mechanisms to relay information about CW performance to their intracellular growth machinery. In the higher plant model Arabidopsis, we previously revealed CW integrity mechanisms that control tip-growth of pollen tubes and root hairs that are governed by the Malectin-like receptor kinase (MLR) subfamily members, namely AtANXUR1/2 (AtANX1/2) and AtFERONIA (AtFER), and a receptor-like cytoplasmic kinase, namely AtMARIS (MRI). Loss-of-function mutants for these CW components lead the growing plant cells to burst spontaneously. Moreover, we showed that these pathways are conserved in the tip-growing rhizoids of the basal land plant Marchantia polymorpha. Marchantia mutants for MpFER and MpMRI, the unique orthologues of AtFER and AtMRI, recapitulate their respective Arabidopsis mutants by displaying rhizoids that also burst during growth. Interestingly, absence of the CW integrity receptor AtFER was shown to render Arabidopsis mutant plants resistance to pathogenic infection indicating that CW integrity mechanisms are subverted by parasitic pathogens to establish disease. Herein, we will present our recent transcriptomics and proteomics analyses of Mpfer and Mpmri to show a remarkable overlap of the up-regulated genes and enriched proteins between the CW integrity mutants and the wild-type Marchantia infected with the oomycete Phytophtora palmivora. Finally, we will exhibit and discuss our preliminary results on the responses of Mpfer and Mpmri to P. palmivora infection.

15 - Ouertani Amira – Axis 2

Deciphering the Molecular Grammar of Condensate Assembly

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Keywords : Post-transcriptional Regulation, C.elegans, Condensates, RNA-RNA interaction, RNA-Protein interaction

Gene expression is coordinated to cellular activity and adapted to stress. At the lowest scale, transcription control can regulate whether an mRNA is transcribed, but it has become evident that rapid, efficient and adaptable responses to cues is achieved by controlling gene expression at the post-transcriptional level. Evidence suggests that post-transcriptional regulation in developing C. elegans oocytes is achieved by RNA binding proteins (RBPs) that dynamically repress maternal mRNAs translation. Recent data from our team further suggests that repressed RNA can be found in (1) a single molecule soluble form that can self-assemble into (2) homotopic clusters that coalesce into (3) larger multiphase heterotypic assemblies with the capacity to reach a higher degree of compaction than DNA in nuclei. However, the mechanism of assembly and function of those different condensates remains an open question. Here I propose to dissect the RNA-RNA interactions that drive condensate assembly, and to test the consequence of RNA condensation on RNA:protein interactions.

16 - Goodluck Benjamin – Axis 3

Nitrogen-Fixing Bacteria Induce Defense Priming Against Pea Aphid In Medicago Truncatula

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Keywords: Nitrogen-fixing symbiosis, Plant Defense, Aphids, Salicylic Acid, Metabolites

Legumes form symbiotic relationships with nitrogen-fixing bacteria, allowing growth in nitrate deficient soils. Legumes are also prone to attacks by herbivores such as the pea aphid (Acyrthosiphon pisum). Beside their nutritional interests, plant-microbe symbioses can induce plant systemic defence reactions against bioagressors. The goal of this work is to study whether nitrogen-fixing symbiosis (NFS) can prime plant defence against pea aphid Acyrthosiphon pisum in the leguminous Medicago truncatula. We analysed the expression of defence genes and metabolite modification in both NFS and nitrate-fed (non-inoculated; NI) conditions with/without aphid infestation. Gene expression analysis showed that plants infested with aphids had significantly higher expression of Pathogenesis Related Protein 1 (PR1), a gene marker of the salicylic acid (SA) pathway, in both NFS and NI conditions. Proteinase Inhibitor (PI), a gene marker of the jasmonic acid (JA) pathway, was also induced by aphid infestation but with significantly higher expression in NFS conditions compared to NI conditions. GC-MS and LC-MS/MS metabolomics showed that 190 metabolites such as salicylate, pipecolate, gentisic acid and various cyclitols and phenols were significantly accumulated upon aphid infestation in the different plant feeding conditions confirming that aphid induced plant defence. Significant accumulation of 20 metabolites in NFS conditions compared to NI conditions suggests a possible immune priming effect on the plant defence by the symbiotic bacteria

17 - Rête Tifenn – Axis 1

RNA granule remodeling in C. elegans germinal tumor

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Keywords : Post-transcriptional regulation, RNA granules, germinal tumor, proliferation, Caenorhabditis elegans

Ribonucleoproteins control maternal RNA expression during germline development. These RBPs target specific mRNAs to repress them in the germline. RNA-RBP complex can sometimes aggregate into a structure called RNA granules. Some of these RBPs, such as CAR -1, are found in every granule, but some RBPs are more stage-specific and control cell fate identity. RBP MEX -3 controls quiescent stem cells, FBF-2 controls proliferative cells, GLD -1 controls cell differentiation, and finally PUF-5 is specific for oocyte differentiation. It has been previously shown that deletion of GLD -1 causes tumors and alters the number and morphology of RNA granules. However, the remodeling of RNA granule composition in germinal tumors is poorly understood.
Our hypothesis is that granule remodeling is involved in tumorigenesis. Here, we have shown that germinal tumor induced by GLD -1 RNAi is followed by ectopic expression of MEX-3 and FBF-2 granules and an increase in granule volume. In contrast, expression of RBP PUF -5 was decreased in the tumor. Subsequently, the pro-proliferative mRNAs such as cyclin B1 were released from the RNA granules during tumor development. Our results allow us to present a new potential model for carcinogenesis involving the RNA granules MEX-3 and FBF-2.

EXPLORATORY STUDY OF SENSORY PERCEPTION OF GRAVITY in Drosophila melanogaster

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Keywords : Gravity, Geotaxis, Mechano-neurons, Sensory organs, Drosophila

Although many animal species use gravity for spatial perception, postural equilibrium, and movement generation, gravity is not easy to sense. The force of gravity is effectively constant, but its vector direction relative to an animal's body varies with body rotation. Therefore, two combined strategies for sensing gravity are integrating directional forces measured across the whole body and/or measuring acceleration at a single point. This means that gravity sensation is extrapolated by combining multisensory information. Due to this integrative nature of gravity perception, the knowledge regarding the molecular and neural basis of gravity sensing is reduced. In Drosophila, a well-studied genetic model of insects, the larva has positive geotaxis in the early stages, which transforms into negative geotaxis in the late stage. Negative geotaxis is defined by a change in larval body orientation and position and is observable when the larva leaves the food source, searching for a suitable pupation site. However, larval gravity perception has never been confirmed or studied. We took advantage of wandering larva/pupe orientation to disclose gravity sensory modality. We used a classical geotaxis assay and screened for sensory organs involved in gravity sensing and geotaxis behavior. Based on current knowledge of the gravitational field, we can assume that a mechanosensory modality will perceive the gravity force. Therefore, we inactivated each mechano-sensory neuron to determine their requirement for larval/pupal orientation. Initially, we identify the larval chordotonal organ as a vital organ for normal geostatic behavior. Gravity sensation in adult flies also requires a chordotonal structure located in the antenna named Johnston's organ, suggesting that ciliated chordotonal organs are a conserved mechanism for gravity perception. Since gravity perception is a multisensory modality, we are currently analysing the contribution of other mechano-neuron/organs as well as the mechanoreceptor involved in its detection. We expect this work to establish the genetic basis for a better understanding of molecular gravity perception.

19 - Simonti Martina – Axis 2

A novel mechanism of non-syndromic Autism Spectrum Disorder caused by mutations of the SCN2A gene: functional studies and knock-in mouse model

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Keywords : Autism spectrum disorder; channelopathies; neurodevelopmental disorder; patch-clamp; behavior

Mutations in the SCN2A gene, encoding the voltage-gated sodium channel Nav1.2, are among those with the strongest association with autism spectrum disorder (ASD). ASD is a neurodevelopmental disorder characterized by social communication deficits, impaired social behavior and stereotypies. It has been observed that ASD-associated SCN2A variants induce a loss of function of Nav1.2, but the pathological mechanism is not clear so far. Recently, a functional study carried out by our team showed that the mutations found in patients with non-syndromic ASD specifically induce a negative dominance in HEK cells and neurons co-expressing WT and mutant channels, leading to an overall >50% reduction of functional Nav1.2 (article in preparation). We generated a new heterozygous knock-in (KI) mouse line carrying one of these mutations, Scn2a-L1314P. 1) Using the patch-clamp technique on brain slices obtained from pups (P5-P9) and young mice (~P25), we are evaluating potential impairments in the medial prefrontal cortex (PFC) layer 5 pyramidal neurons (PYRs) caused by Scn2a-L1314P expression. 2) To determine how these alterations affect the phenotype, we are characterizing mice behavior through a battery of tests, meant to assess ASD core symptoms and comorbidities at young and adult age.

20 - Tanari Abdul Basith – Axis 1

Tuning cytoskeletal and mechanical polarity from the cell to the embryo scale to trigger gastrulation movements

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Keywords : Polarity, Mechanics, Gastrulation, Mechanobiology, Signaling

During embryo development, tissues remodel their shape under the action of biomechanical forces. Contractile networks of F-actin and non-muscle myosin II (MyoII) constitute a primary force-generating machinery in epithelial cells. Embryo-scale polarized force patterns are necessary to initiate coordinated epithelial movements and shape changes. How actomyosin cytoskeleton polarity is tuned at the cell scale to ultimately result in the emergence of embryo- scale polarized force patterns is still poorly understood. To investigate this, we use the early developing Drosophila model system. During the blastula-to-gastrula transition (i.e., during cellularization), the F-actin network and the MyoII distribution is spatio-temporally remodeled and tuned at both the basal and apical sides of epithelial cells establishing a polarized pattern along the embryo dorsal-ventral axis1. For instance, basal MyoII accumulation in ventral cells rapidly vanishes to then reappear apically. This eventually results in a polarized force field driving tissue coordinated movements initiating embryo gastrulation. Here we investigate the cellular mechanisms responsible for fine tuning the F-actin network and the MyoII distribution at basal and apical cell sides. In addition, we investigate how these mechanisms are regulated with high spatio-temporal specificity across the embryo. Finally, by using advanced microscopy, quantitative live image analysis, optogenetics and laser manipulation, this work will shine new light on the mechanisms and the regulatory factors driving actomyosin polarity from the cell to the embryo scale initiating embryo gastrulation.

21 - Teisseire Manon – Axis 3

Targeting CTGF : A new therapeutic strategy in metastatic renal cell carcinoma ?

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Keywords : Anti-angiogenic, renal cell carcinoma, resistance, CTGF

Sunitinib, an oral tyrosine kinase inhibitor, is one of the first line treatment for metastatic renal cell carcinoma (mRCC). Sunitinib prolongs progression-free-survival (PFS) in patients with mRCC. Unfortunately, in most cases, patients relapse after one year of treatment. The anti-angiogenic role of sunitinib on endothelial cells is well described, but its role on tumor cells is poorly understood. We aim to investigate mechanisms of resistance induced by sunitinib on tumor cells. Previous results described sunitinib as a lysosomotropic agent which disrupts autophagy pathway (Giuliano et al., Autophagy, 2015). In the literature, autophagy inhibition creates a pro-inflammatory environment. Proteomic analysis of sunitinib treated and resistant cells to this treatment confirmed an increase in pro-inflammatory proteins and secreted factors in mRCC (Giuliano et al., Theranostics, 2019). Among them, we identified Connective Tissue Growth Factor (CTGF). CTGF is a signaling factor which can promote cancer initiation, progression and metastasis. We demonstrated an increase of CTGF mRNA levels and secreted form in mRCC sunitinib treated and resistant cells. We also demonstrated that CTGF invalidation by siRNA i) induces a cell cycle arrest and decreases proliferation, ii) induces cell death at 96h after transfection, iii) reduces migration and iii) decreases invasion of mRCC cells. Moreover, CTGF recombinant protein increases mRCC cell migration. Our preliminary results indicate that CTGF may play a key role in aggressiveness of mRCC cells and need to be further investigated.

22 - Tleiss Fatima – Axis 1

A TrpA1/DH31-dependent closure of a pylorus-like structure is required for the IMD pathway to kill pathogenic bacteria

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Keywords : IMD pathway, Ros pathway, Drosophila melanogaster, valve, opportunistic bacteria

The body is continuously exposed to damage caused by pathogenic agents, including bacteria. These microbes are in direct contact with the skin, the respiratory system, and the digestive tract, which constitute the interface between the inner body and the environment. The digestive tract is able to fight against foodborne bacteria by three different mechanisms: the physical barrier, the innate immunity and the renewal of the intestine cells. Here, in the intestine of Drosophila melanogaster larva, we uncovered a pylorus-like structure located between the anterior and middle intestine. We showed that the opening and closing of this pylorus was controlled the enteroendocrine DH31 peptides. We further characterized its involvement in the detection and the killing of pathogenic bacteria. Indeed, we observed that as soon as 15 minutes after ingestion of pathogenic bacteria (Gram-positive or Gram-negative) the pylorus closed, blocking the pathogenic bacteria in the anterior part of the intestine. We showed that the blockage was due to production of reactive oxygen species (ROS) that accumulate in the intestinal lumen in response to pathogenic bacteria. Then ROS bound the TRPA1 ion channel receptor in DH31-expressing enteroendocrine cells located in the pylorus. We next demonstrated that this binding triggered the release of the DH31 neuropeptide, inducing the closure of the pylorus and consequently blocking the pathogenic bacteria in the anterior part of the intestine. Finally, we demonstrated that this blocking was necessary to allow the immune deficiency (IMD) pathway to be activated in order to produce antimicrobial peptides (AMPs). These, in turn, killed the bacteria blocked in the anterior part of the intestine, thus insuring the survival of the organism. Conversely, our data indicated that larvae died upon oral infection by pathogenic bacteria when either the ROS/TRPA1 or the IMD pathway was inactivates. Interestingly, the DH31 mammalian ortholog, CGRP, has been identified in enteroendocrine cells located in the rat pylorus (Kasacka; 2009). Therefore, our work shed light on a pylorus-like structure in the Drosophila larval intestine which could serve as a model for studying the functioning and roles of mammalian pylori.

23 - Valero Florian – Axis 2

RNA RNA interaction and condensate assembly

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Keywords : RNA-RNA interaction, RNA-Protein interaction, post-transcriptional regulation, phase separation, membraneless organelles

In the cytosol of eukaryotic cells, the translation of millions of transcripts is adapted to stress. How the translation of these transcripts is coordinated remains to be addressed. Among the post-transcriptional regulations, the translation repression of transcripts is a dynamic process that would allow a rapid and adapted response to a stimulus. Recently, various articles and my team have shown that repressed mRNAs can be found in three forms: (1) in the form of single mRNAs that are soluble in the cytosol; (2) in the form of homotypic clusters of a size at the limit of classic optical resolution; (3) in the form of heterotypic macro-condensates that can reach a size greater than the nucleus which can reach a higher degree of compaction than DNA in the nuclei. The mechanism and function of this aggregation of repressed mRNAs during the stress response, and, the role of the regulatory proteins that control the underlying RNA-RNA interactions, remain to be addressed. Here, using C elegans oocyte response to stress as a model, I propose to map the RNA-RNA interactions that drive RNA condensation, and to dissect the ability of helicases to control these interactions.

24 - Weerasinghe-Arachchige Lahiru-Chamara – Axis 2

Greb1l plays a vital role during the epiblast maturation of mouse embryos.

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Keywords : Greb1l, Embryonic Patterning , Epiblast, Metabolism

GREB1L is a haploinsufficient gene that causes a wide array of congenital abnormalities among human patients. Gene expression analyses on mouse gastrulae revealed that the gene is widely expressed in many progenitor tissues in E7.5 - E8.5 but becomes restricted to the caudal mesoderm and neural progenitors in E9-E10 embryos. In agreement with our gene expression analyses, Greb1l knock-out (KO) embryos develop an axial truncation phenotype at E8.5, which becomes pronounced at E9.
Transcriptomic and immunostaining analysis in E8.5 embryos showed that loss of Greb1l affects several signaling pathways known to be important for proper patterning of the embryo. To understand the specific role of Greb1l during the caudal specification, we performed unbiased approaches of differential proteomic and single cell RNA sequencing (scRNAseq) analyses in E8.25 KO and wildtype littermate embryos. Proteomic analysis revealed KO samples to express significantly lower levels of proteins involved in anterior-posterior patterning, while proteins that play active roles in cell adhesion, lipid metabolism, and hexose metabolism, were found to be higher in KO samples. These results suggest that GREB1L may play a vital role by altering the metabolic status during embryonic patterning.
scRNAseq analyses revealed that gene expression in several developmental clusters diverged in KO embryos, which include the caudal lateral epiblast (CLE), the caudal neuroepithelium, the paraxial mesoderm, and the lateral and intermediate mesoderm. In agreement with our proteomic analysis, KO samples showed a transcriptionally different metabolic signature in several of these clusters. Interestingly, the transcriptional profile of the CLE in KO samples resembled early-stage epiblast cells with high levels of expression of pluripotency markers such as Oct4 (Pou5f1).
Taken together these results demonstrate that Greb1l plays a vital role during early embryogenesis and may suggest that metabolic changes driven by GREB1L expression are required for the differentiation of the epiblast.

25 - Chafik Abderrahman – Axis 3

Control of mitochondrial functions by endosomal GTPase Rab4b-dependent mechanisms

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Keywords : Rab4b, Mitochondria, T cells, Endocytosis

Our team demonstrated that Rab4b, an endosomal Rab GTPase, controls T cell homeostasis in adipose tissue and participates in glucose and lipid homeostasis in mice (Gilleron et al., Cell Rep 2018). The goal is now to understand how Rab4b controls T cell function. Preliminary results indicate that the lack of Rab4b alters mitochondrial function in naive T cells. We, therefore, want to 1) characterize the mitochondrial dysfunction caused by the lack of Rab4b; 2) identify the Rab4b dependent processes responsible for these mitochondrial dysfunctions. To address these objectives, we work on primary CD4+ T cells specifically invalidated for Rab4b using a T cell-specific CRE-Lox system. We studied the mitochondrial activity and mass of CD4+ T cells using fluorescent-specific probes by spectral flow cytometry. We showed that Rab4b-deficient CD4+ T cells had ~20% reduced mitochondrial activity compared to controls without a difference in the mitochondrial mass. Accordingly, experiments using the Seahorse device show that Rab4b-deficient CD4+ T cells have lower respiration. To identify why the down-modulation of Rab4b impacts mitochondrial function, we search by RNAseq for genes differentially expressed between T cells expressing or not Rab4b. Among the 406 genes down-regulated in Rab4b-deficient CD4+ T cells, 26 are mitochondrial. The most impacted gene is Fpgs which encodes the folylpolyglutamate synthetase. This enzyme catalyzes the ATP-dependent addition of glutamate moieties to folate and folate derivatives. Folylpolyglutamates are the intracellular substrates and regulators of one-carbon metabolism, which are involved in nucleotide and amino acids biosynthesis, antioxidant regeneration, and epigenetic regulation. In parallel, we are investigating by electron microscopy the impact of the down-modulation of Rab4b in T cells on mitochondrial morphology, and on putative connections between mitochondria and endosomes. Because Rab4b localization in T cells, particularly in relation to mitochondria, may also be a key element for understanding the mechanism by which Rab4b participates in mitochondrial function, we aim to characterize the localization of Rab4b regarding endosomal compartments and mitochondria. The lack of anti-Rab4b antibodies pushes to generate Knock-In mice with SNAP-tag at the N terminus of Rab4b (SNAP-Rab4b). Western blots showed that the tissue distribution of SNAP-Rab4b is identical to that of its mRNA expression. Histological sections also showed that it is detectable by confocal microscopy. The next steps will be to further characterize the mitochondrial defects in Rab4b-deficient CD4+ T cells, to evaluate the impact of Rab4b-deficiency on metabolic substrate dependency, and to test the relevance of the mitochondrial genes with a Rab4b-dependent expression in the control of mitochondrial function.

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