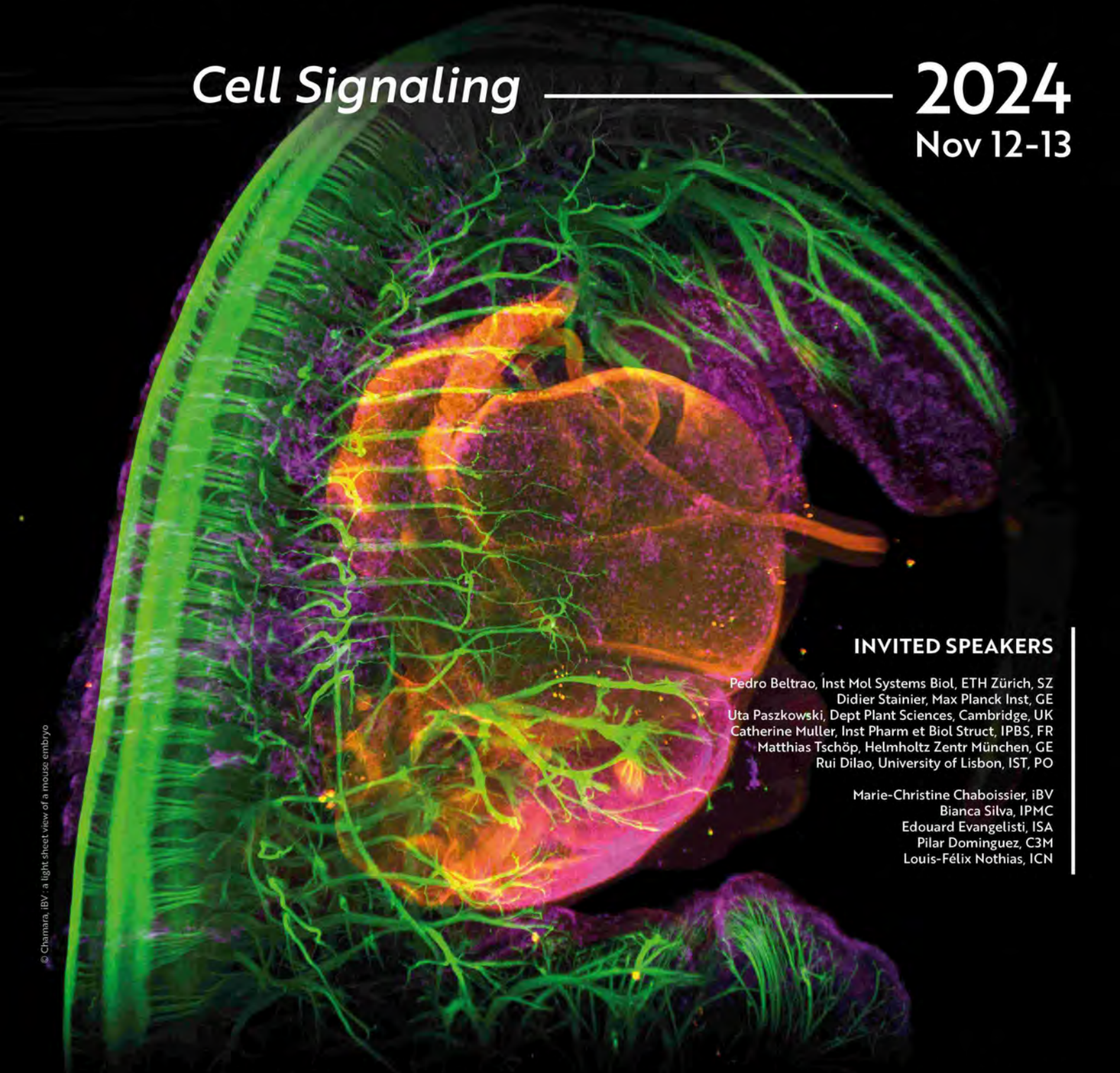
6TH LABEX SIGNALIFE MEETING

Cell Signaling — 2024

Nov 12-13



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INVITED SPEAKERS

Pedro Beltrao, Inst Mol Systems Biol, ETH Zürich, SZ
Didier Stainier, Max Planck Inst, GE
Uta Paszkowski, Dept Plant Sciences, Cambridge, UK
Catherine Muller, Inst Pharm et Biol Struct, IPBS, FR
Matthias Tschöp, Helmholtz Zentr München, GE
Rui Dilao, University of Lisbon, IST, PO

Marie-Christine Chaboissier, iBV
Bianca Silva, IPMC
Edouard Evangelisti, ISA
Pilar Dominguez, C3M
Louis-Félix Nothias, ICN

Le Saint Paul Hôtel
29 bd Franck Pilatte - Nice

Free registration and abstracts
Deadline September 2024, 30th

https://signalife.univ-cotedazur.fr/

UNIVERSITÉ CÔTE D'AZUR · SIGNALIFE · Institut Valrose Biologie · ipmc · IRCAN · Sophia Agrobiotech · Inria · cnrs · INRAE · Inserm · Antoine Lacassagne · chu de Nice

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PROGRAM OVERVIEW

6th labex SIGNALIFE meeting November 12-13th, Le Saint Paul Hôtel, Nice (DAY 1)

	Tuesday, November 12th
12:00-13:00	Poster Session evaluation - Jury only (closed to the public)
13:00-14:00	Registration
14:00-14:15	*Welcome*
	Session I, Axis 1: Cellular Architecture of Signaling Pathways chair: Hélène Barelli (IPMC)
14:15-15:00	*Invited Keynote Lecture:* **Pedro Beltrao**, Inst Molecular Systems Biology, Dept of Biology, ETH Zürich, SZ "Large scale inference of the functional relevance of protein phosphorylation"
15:00-15:30	*SIGNALIFE Keynote* : **Marie-Christine Chaboissier**, iBV "Sex determination: Wt1 drives the female fate"
15:30-15:50	**Elisa Redman**, IPMC "Study of epithelial remodeling in severe asthma using single-cell sequencing approach"
15:50 - 16:10	**Sandra Diaz del Moral**, iBV The expression of the Wilms' tumor suppressor Wt1 in adult cardiomyocytes regulates cellular metabolism & diminishes cardiac damage
16:15-16:45	Group Picture + **Coffee Break**
	Session II, Axis 5: New principles in signaling and applications chair: Madalena Chaves (Inria)
16:45 - 17:30	*Invited Keynote Lecture:* **Rui Dilao**, University of Lisbon, IST, PO "Modelling and calibration of the gene regulatory network of Drosophila early development "
17:30 - 18:00	*SIGNALIFE Keynote:* **Louis-Felix Nothias**, ICN "Discovering Microbially Conjugated Bile Acids with Computational Metabolomics"
18:00 - 18:20	**Marie-Charlotte Dumargne**, IPMC "Effect of weight loss on the epigenetic remodeling of human sperm transposable elements"
18:20 - 18:40	**Florian Valero**, iBV "Coordination of mRNA decay and translation during germline development"
	Poster Session
19:00 - 21:30	**Wine and Cheese Buffet (restaurant) and Poster Session (Chagall Room)**

6th labex SIGNALIFE meeting November 12-13th, Le Saint Paul Hôtel, Nice (DAY 2)

	Wednesday, November 13th
	Session III, Axis 3: Stress Signaling chair: Harald Keller (ISA)
09:00 - 09:45	*Invited Keynote Lecture:* **Uta Paszkowski**, Dept Plant Sciences, University of Cambridge, UK "The Art and Design of Harmony: Molecular Genetics of Arbuscular Mycorrhizal Symbiosis in Cereals"
09:45 - 10:15	*SIGNALIFE Keynote:* **Edouard Evangelisti,** ISA "Signaling puzzle in a filamentous plant pathogen"
10:15 - 10:45	**Coffee Break**
10:45 - 11:05	**Melissa Chapeau**, C3M "Reprogrammed lymph node fibroblasts promote melanoma progression and immune evasion"
11:05 - 11:25	**Sarah Ranty-Roby**, ISA "Manipulation of the plant splicing machinery by MiEFF186, an orphan root-knot nematode effector"
	Session IV, Axis 4: Signaling in aging and disease progression chair: Eric Röttinger (IRCAN)
11:30 - 12:15	*Invited Keynote Lecture:* **Catherine Muller**, Institut de Pharmacologie et de Biologie Structurale, IPBS, FR "Drilling for oil : Tumor-surrounding adipocytes fueling cancer cells to support tumor progression"
12:15 - 12:45	*SIGNALIFE Keynote :* **Pilar Dominguez**, C3M "Epigenetic signaling in blood cancer"
12:45 - 14:00	**Lunch Buffet**
14:00 - 14:45	*Invited Keynote Lecture:* **Matthias Tschöp,** German Research Center for Environemental Health, GE "Overcoming obesity: the discovery of multi receptor drugs"
	Session V, Axis 2: Plasticity and Signaling chair: Matteo Rauzi (iBV)
14:50 - 15:35	*Invited Keynote Lecture:* **Didier Stainier**, Max Planck Institute for Heart and Lung Research, GE "Transcriptional adaptation, an RNA-based mechanism of genetic compensation"
15:35 - 16:05	*SIGNALIFE Keynote :* **Bianca Silva**, IPMC "Brain circuits of Memory Update"
16:05 - 16:40	**Coffee Break**
16:40 - 17:00	**Brice Angot**, C3M "Role of the mechano-sensitive ion channel Piezo1 in the regulation of the metabolism of the thermogenic brown adipocytes"
17:00- 17:20	**Oceane Bouvet**, C3M "Role of collagen receptors DDR1/2 in metabolic adaptation of dedifferentiated melanoma cells to extracellular mechanical signals"
17:20 - 17:45	*Poster and Oral Communication Awards*
17:45 - 18:00	*Concluding remarks*
19:30-23:00	**Gala diner at the Hôtel restaurant**

ORAL COMMUNICATIONS

Session I, Axis 1
Cellular Architecture of Signaling Pathways

Chair : H. Barelli

Invited Keynote Lecture : Pedro Beltrao

Large scale inference of the functional relevance of protein phosphorylation

Pedro Beltrao

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Keywords : kinase signalling, bioinformatics, cancer

Cells need to constantly adapt to changes in conditions and use post-translational regulation as a fast way to transfer information from sensors to effectors of cellular responses. Advances in mass-spectrometry allow us to identify post-translational modification (PTMs) sites on a large scale and to quantify their changes across different conditions. However, the interpretation of these measured changes remains challenging as we don't know the functional role of most human phosphosites. We have worked on approaches that try to predict the which phosphorylation are most important to cells and how to use large scale phosphoproteomics to infer the activation state of kinases. As an example we have applied these approaches to study the changes in kinase signalling across tumour samples revealing which kinases are most often regulated in different tumour types with some linked with patient survival. We also see a disconnect between the mutational status of the tumour and the predicted activation state of kinases, indicating substantial compensatory mechanisms. More recently we have been working on computational methods to predict the biological process (e.g. DNA repair, cell-cycle) that is regulated by specific phosphosites allowing us to propose regulatory functions across the human proteome. These approaches are starting to give us a less biased understanding of the kinase signalling network and uncovering the importance of phospho-regulation across multiple aspects of cell biology and disease.

Signalife Keynote : Marie-Christine Chaboissier

Sex determination: Wt1 drives the female fate.

Elodie Gregoire, Marie-Cécile De Cian, Aitana Perea-Gomez, Natividad Bellido-Carreras, Isabelle Gillot, Mélanie Detti, Magali Dhellemmes, Yasmine Neirijnck, Andreas Schedl and Marie-Christine Chaboissier

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Keywords : Sex determination, gonad development, ovarian-determinant, disorders of sex development, genome editing

In most mammals, the sex of an individual is determined at the time of fertilization by the paternal transmission of the X or Y sex chromosome and the maternal transmission of an X chromosome. This is the process of sex determination that initiates the sexual differentiation of the embryo, promoting the development of the bipotential gonad into a testis in the XY embryo and an ovary in the XX embryo. The testis determinant was identified in the early 1990s as the SRY gene, located on the Y chromosome. This gene is both necessary and sufficient to initiate the male developmental programme. It took over 30 years to identify the factor responsible for initiating ovarian differentiation, which turned out to be a variant produced by alternative splicing of the Wilms' tumour suppressor gene, WT1. This isoform is known as -KTS, in contrast to the +KTS isoform, which includes three additional amino acids: lysine, threonine, and serine. We have shown that -KTS is required to induce ovarian development in XX mice and can prevent male development when it is prematurely activated in XY embryos. In humans, an imbalance of the +KTS/-KTS ratio in favor of -KTS is responsible for Frasier syndrome in patients with a 46,XY karyotype who suffer from glomerular nephropathy and gonadal dysgenesis. Our results have led to a revision of the model of sex determination, a process driven by two specific sex determinants, SRY for males and WT1-KTS for females.

Presentation 1: Elisa Redman

Study of epithelial remodeling in severe asthma using single-cell sequencing approach

Redman E.*1,2 ; Fierville M.1,2,3 ; Gras D.4 ; Valette K.4,5 ; Porracciolo P.1,2 ; Leroy S.2,6 ; Couralet M. 1,2 ; Chanez P.4,5 ; Barbry P.1,2,6 ; Zaragosi LE.1,2

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Keywords : Single-cell RNA seq, Asthma, Airway, Epithelial, Regeneration

The airway surface epithelium is a complex cellular ecosystem that includes basal, goblet and multiciliated cells. Motile cilia on multiciliated cells clear the pathogen-trapping mucus secreted by goblet cells in a process called mucociliary clearance. In asthma, the epithelium undergoes chronic inflammation and remodeling, which results in fewer multiciliated cells and a goblet cell hyperplasia that impairs mucociliary clearance and worsen symptoms. Interleukin 13 (IL-13), produced by type-2 lymphocyte T helper (Th2) cells, is a major mediator of type 2 high asthma, the most common endotype. IL-13 directly causes goblet cell hyperplasia and can be used in vitro to induce asthma-like remodeling, but the effects of this cytokine on epithelia obtained from healthy donors and severe asthmatics have never been compared. Moreover, the cellular and molecular events enabling epithelial regeneration in this context remain unexplored. Thus, the aim of this study was to identify the key players in the pathological remodeling of the airway epithelium in severe asthma. The study involved epithelia reconstituted in vitro, in an air-liquid interface culture model, from bronchial biopsies from healthy or severe asthmatic donors. After 8 (D8) or 22 days (D22) of apical IL-13 treatment, epithelia were analyzed by confocal imaging and single-cell RNA sequencing. A second observation was done two weeks after IL-13 withdrawal to mimic local inflammation resolution. The involvement of two genes in epithelial remodeling was studied after their invalidation by CRISPR-Cas9 and analysis by single-cell RNA sequencing. Over 260,000 cells from 9 healthy and 11 severe asthmatic donors were studied. Epithelia from severe asthmatics showed baseline basal cell hyperplasia and a cell differentiation defect with luminal expression of keratins KRT5, KRT6A and KRT16. IL-13 induced, in the epithelia of severe asthmatics, a two-stage remodeling process with initial goblet cell hyperplasia (D8), followed by basal cell hyperplasia at D22. Two weeks after withdrawal of IL-13, the recovery capacities between healthy cells and cells from severe asthmatics appeared similar. Follow-up confocal microscopy and cell trajectory inference analyses identified a population of hybrid cells expressing both multiciliated (FOXJ1) and goblet cell (SPDEF) markers, whose origin appears to be the multiciliated cells. Our transcriptomic analysis yielded a list of genes likely to regulate epithelial remodeling. The effect of CRISPR-Cas9-mediated invalidation of two of these genes, EHF and GATA3, was assessed by single-cell RNA sequencing. This study highlights defects in epithelial cell differentiation in severe asthmatics at baseline with overexpression of basal markers and distinct processes of IL13-mediated remodeling. The identification of FOXJ1+/SPDEF+ hybrid cells suggests a possible contribution of cellular transdifferentiation events to the dysregulation of tissue composition and function.

Presentation 2: Sandra Díaz del Moral

The expression of the Wilms' tumor suppressor Wt1 in adult cardiomyocytes regulates cellular metabolism and diminishes cardiac damage

Sandra Díaz del Moral; Nicole Wagner; Maha Benaouicha; Rita Carmona; Ramón Muñoz-Chápuli; Kay-Dietrich Wagner

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Keywords : Cardiomyocyte; Wilms' tumor suppressor Wt1; Metabolism; Doxorubicin; Damage

The Wilms' tumor suppressor Wt1 is involved in cardiac development as well as in heart homeostasis and repair. Wt1 encodes a zinc-finger transcription factor that participates in the development of several other organs, including the kidneys and spleen. In the heart, Wt1 expression has been identified in smooth muscle cells, fibroblasts, epicardial and endothelial cells, and more recently, in embryonic and adult cardiomyocytes. Murine embryos carrying the cardiomyocyte-specific Wt1 deletion showed irregular heart development, with abnormal atrium and sinus venosus development, thin ventricular myocardium and lack of pectinate muscles, and electrocardiographic anomalies in the surviving adults. Re-expression of Wt1 after myocardial infarction in cardiomyocytes located in the border zone has been also described. For these reasons, we wanted to study in depth the role of Wt1 in cardiomyocytes, and the consequences of its conditional deletion in homeostatic conditions and in response to pharmacologically induced damaged by doxorubicin administration. Wt1 silencing was performed in isolated neonatal cardiomyocytes using lentiviral particles expressing Wt1 short hairpin RNA. For conditional deletion of Wt1 in adult cardiomyocytes, tamoxifen inducible αMHCMerCreMer mice were crossed with homozygous WT1-floxed mice. In addition, doxorubicin was administered to groups of control and Wt1-deleted mice. We observed that silencing of Wt1 in cultured neonatal cardiomyocytes changes the expression of genes related to calcium homeostasis and alters mitochondrial membrane potential. Wt1 ablation in adult cardiomyocytes caused hypertrophy, interstitial fibrosis, mitochondrial dysfunction and altered metabolism, that included abnormal fatty acid metabolism, and downregulation of the oxidative phosphorylation and the electron transport chain pathways. Currently, we investigate direct transcriptional target genes of Wt1 related to cardiac metabolism, which might be relevant for repair. The lack of Wt1 expression in adult cardiomyocytes increased doxorubicin-induced damaged after either acute or chronic exposure. Taken together, these results show that Wt1 expression is crucial in adult cardiomyocytes, demonstrating a novel role of Wt1 in the metabolism of cardiomyocytes, and in their protection against cardiotoxic damage.

Session II, Axis 5

New principles in signaling and applications

Chair : M. Chaves

Invited Keynote Lecture : Rui Dilão

Modelling and calibration of the gene regulatory network of Drosophila early development

Rui Dilão

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Keywords : Morphogenesis, Drosophila early development, pair-rule proteins, segment-polarity proteins

One of the characteristics of arthropods (insects, spiders, centipedes, shrimps, trilobites, etc.) is the formation, during the first hours of development, of protein bands along the embryo's surface layer, expressed perpendicular to the anteroposterior axis of the embryo. In Drosophila, during the first two hours of the larval stage development, in the syncytial phase, protein bands are classified into four families — maternal, gap, pair-rule and segment-polarity proteins. After this phase, cellularisation occurs, and different body cells have different protein contents, leading to specialised body parts. Here, we present the modelling, calibration and validation of the gene regulatory networks associated with each of the four classes of Drosophila syncytial proteins. The maternal and gap proteins auto-cis-regulate during the first 13 nuclear cycles, and segmentation occurs due to a Turing-type reaction-diffusion process involving mRNAs. We show that, during the 14th nuclear cycle, the pair-rule proteins Even-skipped (Eve) and Fushi-tarazu (Ftz) are negatively regulated by several gap proteins with embryo position-dependent activation rates, leading to the stable 7 strip segments characteristics of Eve and Ftz. We provide evidence that the segment-polarity protein Wingless (Wg) may be negatively regulated by Eve and Ftz, leading to the stable 14 Wg strip segments. The patterns of the loss-of-function mutants validated all the calibrated models. Finally, we propose a list of open problems in the Drosophila's biology.
References: F. Alves and R. Dilão, A simple framework to describe the regulation of gene expression in prokaryotes, C. R. Biologies 328 (2005) 429-444. F. Alves and R. Dilão, Modeling segmental patterning in Drosophila: maternal and gap genes, J. Theo. Biol. 241 (2006) 342-359. R. Dilão, D. Muraro, M. Nicolau and M. Schoenauer, Validation of a morphogenesis model of Drosophila early development by a multi-objective evolutionary optimization algorithm. In C. Pizzuti, M.D. Ritchie, and M. Giacobini (eds.), "Evolutionary Computation, Machine Learning and Data Mining in Bioinformatics", Lecture Notes in Computer Science Vol. 5483, pp. 176-190, 2009. R. Dilão and D. Muraro, mRNA diffusion explains protein gradients in Drosophila early development, J. Theo. Biol. 264 (2010) 847-853. R. Dilão and D. Muraro, Calibration and validation of a genetic regulatory network model describing the production of the protein Hunchback in Drosophila early development, C. R. Biologies 333 (2010) 779-788. R. Dilão and D. Muraro, A Software Tool to Model Genetic Regulatory Networks. Applications to the Modeling of Threshold Phenomena and of Spatial Patterning in Drosophila, PLOS ONE 5, 1-10. D. Muraro and R. Dilão, A parallel multi-objective optimization algorithm for the calibration of mathematical models, Swarm and Evolutionary Computation, 8 (2013) 13-25. R. Dilão, Bicoid mRNA diffusion as a mechanism of morphogenesis in Dr

Signalife Keynote : Louis-Félix Nothias

Discovering Microbially Conjugated Bile Acids with Computational Metabolomics

Louis-Félix Nothias[1,2]

(1) University Côte d'Azur, CNRS, ICN, Nice, France
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Keywords : Metabolomics, Mass spectrometry, Microbially-Conjugated Bile acids

Advancements in mass spectrometry and computational metabolomics have significantly enhanced our understanding of the complex interplay between the gut microbiome and host metabolism. In recent years, these techniques have been successfully employed by researchers to uncover the extent of novel bile acid conjugates produced by the human gut microbiome. In this SIGNALIFE keynote, I will present these discoveries, discuss their biological and chemical implications, and describe the innovative experimental and computational developments that enabled these findings. This includes our integrative approach combining combinatorial chemistry with deep learning, as well as our preliminary translational analyses using public data repositories (Hoffmann, Nothias, Ludwig, et al., *Nature Biotechnology*, 40, 411–421, 2022). I will conclude by introducing our ongoing efforts to develop next-generation AI systems that can accelerate molecular omics education and data mining through intuitive, dialogue-based interfaces, thereby promoting discovery and innovation in the field.

Presentation 1: Marie-Charlotte Dumargne

Effect of weight loss on the epigenetic remodeling of human sperm transposable elements

Marie-Charlotte Dumargne, Romain Barrès

(1) Institut de pharmacologie moléculaire et cellulaire

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Keywords : Obesity, weight loss, spermatozoa, epigenetic inheritance, transposable elements

In 2023, nearly half of French adults were overweight or obese. European surveys recently reported that despite being on a diet, 70% of the people attempting to lose weight in the past 12 months did not achieve clinically meaningful weight loss. Transposable elements (TEs), commonly referred to as jumping genes, occupy more than half of the human genome. Their mobility generates structural variation with potential pathogenic consequences when their insertion disrupts important genes functions. Human sperm TEs escape DNA methylation reprogramming during gametogenesis and therefore carry potential to transmit epigenetic information from one generation to the next. Given the acceleration of obesity prevalence, we hypothesize that insertions of TE and/or epigenetic remodeling participate in the obesity pandemic. More particularly, we hypothesize that obesity spurs mobile elements activity which in turn leaves an epigenetic imprint on their jumping way that predispose the offspring genomic make-up to easier weight gain. To characterize the effects of a diet-induced weight loss on the human sperm young transposable elements, we sequenced the sperm of men with obesity using long-read Oxford Nanopore sequencing. We detected 1,549 TE insertions of the most actives sub-families, which affected 591 genes. Among these, 21 were in promoters or exons and 570 were introners. Potential functional impact was evaluated with gene annotation and enrichment analysis, which suggested a strong relationship with genes involved in lipid and carbohydrate metabolism, muscle process and neurogenesis. As spermatozoa are haploid, the sequencing reads directly correspond to the fraction of cells carrying a TE insertion at that position. Comparison from before versus after weight loss revealed that TE insertions were never present in all reads and tended to decrease after the diet intervention suggesting that TE insertions only occur in a subpopulation of spermatozoa. The type of structural variants (insertion, deletion, inversion, duplication or translocation) and the tissue origin (germline, de novo or somatic) are currently being explored and will be presented.

Presentation 2: Florian Valero

Coordination of mRNA decay and translation during germline development

Florian Valero, Amira Ouertani, Chloé Leray, Karine Jacquet, Delphine Ciais, Solène Bruni-Favier, Sami Rouquet, Arnaud Hubstenberger

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Keywords : RNAi, C. elegans, Decay, Translation, Post-transcriptional regulation

The post-transcriptional regulations of gene expression involve mRNA decay and mRNA translation control, which both impact the protein production outcome. We and others have uncovered how the regulatory pathways that control alternative mRNA fates, such as storage or decay, translation or repression, are often compartmentalized in membraneless organelles termed RNA condensates (Cardona et al., Cell, 2023). However, despite advances in understanding the compartmentalization of post-transcriptional regulations, how the controls of mRNA decay and mRNA translation are coordinated remain poorly understood. Here, using C. elegans germline as a model, where mRNAs are sequentially translated and repressed to control oocyte development, I investigated how the mRNA translation status impacts the mRNA sensitivity to RNAi decay, and I tested how mRNA sub-cellular compartmentalization participates to these mRNA controls. To address these questions, I needed to circumvent a technical challenge: measuring mRNA decay with single copy sensitivity, and simultaneously localizing mRNAs with subcellular resolution. For that purpose, I successfully adapted a single molecule Fluorescent In Situ Hybridization (smFISH) approach. Thus, I could distinguish mRNAs localizing in storage bodies from translated mRNAs dispersed through the cytosol, or quantify the mRNA pool localizing to RNAi amplifying bodies, while recording in parallel mRNA decay rates. Thus, I could demonstrate that (1) mRNAs that are cytosolic and translated are hypersensitive to RNAi decay, (2) mRNAs that repressed and condensed in P-bodies reservoirs resist to decay, (3) mRNA accumulation in RNAi amplifying bodies is complementary to the mRNA repression patterns. Furthermore, the analysis of diverse mRNAs with complementary expression patterns across the oogenesis cell cycle, suggests that the connections between cytosolic mRNA translation and RNAi decay sensitivity, as well as the connection between mRNA repression and RNAi amplification, are conserved throughout the cycle progression and can be generalized for a wide diversity of transcripts. I am currently further dissecting the molecular players that coordinate (1) mRNA translation to decay and (2) mRNA repression to RNAi amplification. Altogether, we provide new insights on how mRNA translation, subcellular localization and decay are coordinated to control protein production across oocyte development.

Session III, Axis 3
Stress Signaling

Chair : H. Keller

Invited Keynote Lecture : Uta Paszkowski

The Art and Design of Harmony: Molecular Genetics of Arbuscular Mycorrhizal Symbiosis in Cereals

UTA PASZKOWSKI

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Keywords : cereals, symbiosis, fungi, signalling, plant nutrition

The arbuscular mycorrhizal (AM) symbiosis is a fascinating mutualistic interaction between roots of most land plants and fungi of the phylum of the Glomeromycota. The development of this life-long alliance starts with reciprocal recognition in the rhizosphere, reprogramming both symbionts for the anticipated association. The interaction proceeds towards extensive root colonization which culminates in the formation of fungal feeding structures, the arbuscules, inside root cortex cells. As the arbuscule develops, the plant cell dramatically increases membrane biogenesis to envelope the growing hyphal structure. Thereby a hugely enlarged intracellular surface area is created between the two organisms, appearing ideally adapted for the exchange of signals and nutrients. The nature and complexity of the establishment of AM symbioses must be the result of a well-orchestrated exchange of molecular signals between the plant and the fungus. The nature of some of the signals has been discovered in recent years, providing a first insight into the type of chemical language spoken between the two symbiotic partners. My group has taken molecular genetics and lately advanced imaging approaches to elucidate the molecular mechanisms underpinning this apparently harmonious symbiosis. I will introduce some of our recent observations which have led us to propose fundamentally new communication mechanisms operating during this intimate plant-fungal partnership.

Signalife Keynote : Edouard Evangelisti

Signaling puzzle in a filamentous plant pathogen

EDOUARD EVANGELISTI

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(*corresponding author : edouard.evangelisti@inrae.fr*)

Keywords : Stramenopiles, oomycetes, signalling, plant pathogens, virulence, secretion

Life is hard for look-alikes, and oomycetes know this all too well. Often mistaken for fungi due to their filamentous growth, they frequently occupy similar ecological niches. Like fungi, some have emerged as prominent plant pathogens that pose serious threats to global food security and ecosystem resilience. Yet, despite these similarities, oomycetes are more distantly related to fungi than animals are to plants, instead sharing closer evolutionary ties with organisms such as brown algae and apicomplexans, including malaria parasites. This evolutionary distance profoundly influences how they infect plants, deliver virulence factors, and organize at the cellular level. Recent research has begun illuminating the commonalities and unique aspects of oomycete physiology, positioning them as valuable models for studying molecular signalling and cellular organization. This talk will highlight critical advances in oomycete biology and explore the challenges that lie ahead in fully unravelling the molecular basis of their pathogenicity.

Presentation 1: Mélissa Chapeau

Reprogrammed lymph node fibroblasts promote melanoma progression and immune evasion

M. Chapeau, C. Rovera, C. Tavernier, L. Delhaye, D. Graça, A. Carminati, F. Larbret, M. Irondelle, M. Deckert, S. Tartare-Deckert, V. Prod'Homme

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Keywords : Melanoma, Fibroblastic Reticular Cells, lymph node, pre-metastatic education, T cells

Melanoma is an aggressive skin cancer arising from the malignant transformation of melanocytes, the cells responsible for skin pigmentation. When localized in the skin, melanoma is treatable by surgical resection; however, if it is not detected early, it will invariably metastasize, starting by invading the lymph nodes. This lymphatic invasion is a critical step in melanoma progression, as it allows cancer cells to enter the bloodstream and spread to other organs such as the liver, bones, lungs, and brain. Understanding the mechanisms underlying lymph node invasion could lead to earlier and more effective interventions. During the pre-metastatic phase, lymph nodes are reprogrammed by factors secreted by melanoma cells in the skin, creating a niche favorable to tumor invasion and proliferation. During this phase, lymph node fibroblasts, known as Fibroblastic Reticular Cells (FRCs), are reprogrammed. In healthy lymph nodes, FRCs play a key role in organizing the structure of lymph nodes and in regulating T cell recruitment, survival, and activation. In many tissues, fibroblasts in the tumor microenvironment, also known as cancer-associated fibroblasts, are known to promote cancer progression, but little is known about the role of FRCs in the lymph node. Previous work by my team demonstrated that dedifferentiated melanoma cells inhibit the contractility of FRCs, thereby facilitating melanoma cell invasion. My research reveals that reprogrammed FRCs also enhance the proliferation of tumor cells and their resistance to targeted therapies used in the clinic. Additionally, these reprogrammed FRCs disrupt the anti-tumor immune response by altering T cell motility, activation, and upregulating immune checkpoint molecules (PD1, LAG3, and CTLA4) on T cells. These findings highlight the critical role of FRCs in early melanoma progression, suggesting new therapeutic approaches based on targeting FRCs in the lymph nodes.

Presentation 2: Sarah Ranty-Roby

Manipulation of the plant splicing machinery by MiEFF186, an orphan root-knot nematode effector

Ranty-Roby S.1, Mulet K. 1, Soulé S. 1, Caravel C. 1, Favery B. 1, and Quentin, M1

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Keywords : Root knot nematodes, Effectors, Alternative splicing, CIS2/GDP1, Giant cells

Plant parasitic nematodes are microscopic worms. Root-knot nematodes (RKNs), the most damaging species, have adopted a sedentary lifestyle within their hosts. These obligate endoparasites are biotrophs that induce the differentiation of root cells into hypertrophied and multinucleate giant feeding cells which are essential for their development and the disease propagation. Effector proteins produced in oesophageal glands of the RKNs and secreted *in planta* through a syringe-like stylet, are instrumental in hijacking host cellular processes and enabling giant cell development and maintenance.
A combination of comparative genomics and transcriptomics allowed the identification of a repertoire of putative RKN effectors. We identified a gene (*MiEFF186*) specifically expressed in the esophageal glands of parasitic juveniles that encode a protein targeting the plant cell nucleus and suggest modulation of host alternative splicing. Using a yeast two-hybrid approach, we identified a splicing factor, CIS2/GDP1, as a major host target of MiEFF186. *Arabidopsis* mutants affected in this gene and silencing of this target in tobacco significantly impacted plant susceptibility to the nematode. We aim to better understand how MiEFF186 effector modulate alternative splicing to allow transcriptional reprogramming of vascular root cells and giant cells formation.

Session IV, Axis 4
Signaling in aging and disease progression

Chair : E. Röttinger

Invited Keynote Lecture : Catherine Muller-Staumont

Drilling for oil : Tumor-surrounding adipocytes fueling cancer cells to support tumor progression

Pr Catherine MULLER-STAUMONT

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Keywords : adipocytes, obesity, cancer, cell metabolism, invasion

Lipid-filled mature adipocytes are frequently found in proximity to invasive human solid tumors such as breast and prostate cancers. At the tumor invasive front, adipocytes exhibit a decrease in size and lipid content, cells that we named Cancer associated Adipocytes (CAAs) (Dirat et al, Cancer Research, 2011). We further shown that CAAs release free fatty acids (FFAs) or fatty acids contained in extra-cellular vesicles and that these FFAs are taken up by tumor cells and used to promote tumor progression by mechanisms that include, but is not limited to, mitochondrial fatty acid oxidation (FAO) (Wang et al, JCI insight, 2017 ; Laurent et al, Molecular Cancer Research, 2019; Clement et al, EMBO J, 2020). I will discuss recent advances in our understanding of this metabolic symbiosis between adipocytes and cancer cells and underlines the differences in this metabolic crosstalk between the various types of cancer and their localization (including bone metastasis where the adipocytes present at proximity of cancer cells exhibit a peculiar phenotype, Attané et al, Cell Reports, 2020). The known association between obesity and cancer mortality clearly reinforces interest in this research area. Obesity is characterized by increased adipose depot size associated with changes at tissue level, including for adipocytes increased in lipid content and metabolic dysfunctions. We will see the emerging results showing that this state could affect metabolic symbiosis between tumor-surrounding adipocytes and cancer cells. Once well established, the metabolic symbiosis between cancer cells and adipocytes will undoubtedly offer new therapeutic avenues in the treatment of cancer in obese and nonobese patients.

Signalife Keynote : Pilar Dominguez

Epigenetic signaling in blood cancer

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Keywords : Lymphoma, epigenetics, targeted drugs, combinatorial therapy

Our team Cancer Epigeneics and Imunotherapy (CEPIMMY) focuses on hematological malignancies (lymphoma, leukemia), common and aggressive cancers with limited treatment options based on chemotherapy. One main characteristic of blood cancers is the presence of mutations in epigenetic proteins and previous studies have clearly demonstrated that perturbation of the epigenetic programming is strongly linked to the genesis and pathogenesis of these types of cancers. Therefore, therapies aimed at reversing malfunctioning epigenetic mechanisms are expected to be beneficial for patients with hematological tumors. However, while certain epigenetic therapies are used as anti-cancer treatments, their full potential has not been achieved. Our goal is to improve and expand the application of epigenetic-based drugs to treat lymphoma and leukemia. I will present published and unpublished results from our three research axes: 1) to investigate the mechanistic events underpinning the development and progression of blood cancers caused by malfunctioning of epigenetic processes (Cancer Discovery, 2018; Science Advances, 2020); 2) to understand how epigenetic mechanisms modulate the dynamic cellular interactions between the tumor and the immune system (Cancer Discovery, 2022) and 3) to explore new combinatorial epigenetic therapies (unpublished data).

Invited Keynote Lecture : Matthias Tschöp

Overcoming Obesity: The Discovery of Multi Receptor Drugs

Matthias Tschöp

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Keywords : Precision therapeutics; metabolic diseases; diabetes and obesity research

On our mission to overcome the obesity pandemic by discovering highly effective medicines, we hypothesized that chemistry based on more than one endocrine factor may be required to significantly reduce body fat without causing severe side effects. We selected combinations of afferent gut hormones acting in the CNS as the most likely path toward efficacy comparable to bariatric surgery benefits. Over the last 20 years, we combined advanced in vivo preclinical biology with state-of-the-art peptide chemistry to achieve such synergistic gastrointestinal hormone pharmacology. What proved successful was the unprecedented approach of fully integrating two and three mechanisms of biological action at a potency that matched the individual native hormones into single molecules. The resulting peptides are analogous to master keys, structurally nearly identical to natural gut hormones, but delivering multiple metabolic action profiles. We discovered multiple dual and triple hormone-like chimeric peptides from a set of intestinal hormones and chemically refined these for medicinal purposes to possess suitable time action and physical properties to support infrequent subcutaneous dosing. This new class of drugs was then validated by showing unprecedented improvements in glycemic control and body weight reduction in multiple rodent models of obesity and insulin resistance. Aiming at efficient translation into clinical medicine, we designed and supervised the validation of the rodent observation with first-generation forms of these poly-agonists in non-human primate studies and subsequently in the first clinical trials. The results triggered numerous pharmaceutical interests and led to multiple competitive dual and triple agonist versions now advancing in mid and late-stage clinical trials, reflecting medicinal importance of the discovery and validating the reproducibility of their pioneering science. Tirzepatide/Mounjaro (Eli Lilly & Co) represents one of the initial members of the newly discovered class of dual agonist drugs and was FDA-approved last year for treating type 2 diabetes. It synergistically integrates GIP and GLP-1 receptor agonist pharmacology into a single molecule, as we had first discovered and reported in 2013. The GIP/GLP-1 dual agonist Tirzepatide/Mounjaro achieves an average of 22.5% weight loss in clinical obesity, a milestone achievement previously thought to be impossible. Regulatory approval of Mounjaro for treating obesity is imminent and several other versions of these dual and triple agonist classes of drugs are successfully underway through clinical phase I, II and III trials.

Session V, Axis 2
Plasticity and Signaling

Chair : M. Rauzi

Invited Keynote Lecture : Didier Stainier

Transcriptional adaptation, an RNA-based mechanism of genetic compensation

Didier Stainier, Lara Falcucci, Chris Dooley, Kuan-Lun Hsu, Gabriel Jakutis, Brian Juvik, Vahan Serobyan, Jordan Welker, Lihan Xie, Jie Liang, Cansu Cirzi, Nana Fukuda, Charlie Song, Hamzeh Haj-Hammedeh, Mikhail Sharkov, Greta Ebnicher, Pankaj Kumar; Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

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Keywords : Transcriptional adaptation, RNA, genetic compensation, gene regulation, mRNA decay

Each human genome has been reported to contain approximately 100 loss-of-function variants, with roughly 20 genes completely inactivated. Some of these completely inactivated genes are essential genes, and yet they are present in a homozygous state in apparently healthy individuals. This totally unexpected lack of phenotype has also been observed in commonly studied model organisms from yeast to mammals. Various hypotheses have been proposed to explain these findings including Genetic Compensation (GC). GC manifests itself as altered gene/protein expression, or function, which leads to a wild-type-like phenotype in homozygous mutant or heterozygous individuals who would be predicted to exhibit clear defects. Traditionally, GC has been thought to involve protein feedback loops such that if one component of a regulatory pathway is deficient, a compensatory rewiring within a network or the activation of a functionally redundant gene occurs. However, not every major regulatory network has evolved to incorporate such complex features. Another mechanism of GC is the newly identified process of Transcriptional Adaptation (TA): some deleterious mutations, but not all, trigger the transcriptional modulation of so-called adapting genes. Depending on the nature of these adapting genes, GC can occur. Notably, unlike other mechanisms underlying genetic robustness, TA is not triggered by the loss of protein function.

We discovered TA while trying to understand the phenotypic differences between knockout (mutant) and knockdown (morphant) zebrafish embryos. Further studies identified additional examples of TA in zebrafish as well as examples in *C. elegans* and in mammalian cell lines. By generating and analyzing several mutant alleles for these genes, including non-transcribing alleles, we found that the mutant mRNA is required to trigger TA. Based on these and other data, we hypothesize that all mutations that cause mutant mRNA degradation can trigger TA. The current model is that mutant mRNA degradation fragments translocate back to the nucleus where they modulate gene expression. Key questions about TA include the identity of the adapting genes and the mechanisms underlying their transcriptional modulation. This presentation will go over our published and unpublished data on TA in several model systems including zebrafish, *C. elegans*, *Neurospora*, and mammalian cells in culture. Additional data will explore therapeutic applications for TA.

Signalife Keynote : Bianca A. Silva

Brain Circuits of Memory Update

Bianca A. Silva

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Keywords : Neuroscience, PTSD, Whole-bran imaging, memory networks, fear circuits

How are consolidated memories modified on the basis of experience? Understanding this biological process allows us to decipher how new information is constantly incorporated into existing memory, how a newly formed memory is integrated into previous knowledge and how the fine balance between memory stability and memory flexibility is maintained.
By using fear memory extinction as a model of memory update, we combined neuronal circuit mapping, fiber photometry, chemogenetic and closed-loop optogenetic manipulations in mice, and showed that the extinction of remote (30-day old) fear memories depends on thalamic nucleus reuniens (NRe) inputs to the basolateral amygdala (BLA). These findings identify the NRe as a crucial BLA regulator for extinction, and provide the first functional description of the circuits underlying the experience-based modification of consolidated fear memories.
We are now using whole-brain circuit tracing and activity mapping to investigate how this NRe-centred circuit is organized at the brain-wide level and how it is affected by pathological conditions characterized by extinction deficits.

Presentation 1: Brice Angot

Role of the mechano-sensitive ion channel Piezo1 in the regulation of the metabolism of the thermogenic brown adipocytes

Brice ANGOT, Malika ARHATTE, Pierre-Louis BATROW, Isabelle SATNEY, Jérôme GILLERON, Étienne, MOUISEL, Dominique LANGIN, Mireille CORMONT, Ez-Zoubir AMRI Éric HONORÉ, Jean-François TANTI

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Keywords : Obesity, fat mass, metabolism, thermogenesis, mechanotransduction

Obesity has reached epidemic proportions, leading to serious cardiometabolic disease. Imbalance between energy intake and expenditure is the main driver of obesity and increasing energy expenditure is a strategy to reduce body weight. Brown adipocytes (BA) in brown adipose tissue (BAT) are thermogenic adipocytes that dissipate excess energy as heat, termed non-shivering thermogenesis, thanks to the uncoupling protein UCP1 expressed in their mitochondria. Glucose and lipids provide fuel to support uncoupled respiration. BA are activated by sympathetic nerves in response to various stimuli such as cold or food intake and pharmacologically by beta-adrenergic receptor agonist. BA activation increases energy expenditure reducing body weight and improves glucose and lipid metabolism, and insulin sensitivity. A better understanding of the protein network controlling BA activation may therefore identify new targets to combat obesity. BA have been shown to be mechanosensitive, suggesting that mechanosensors regulate their function. As mechanosensitive ion channels are early players in mechanosensing, we investigated whether such channels were expressed in BA and their regulation and role. We showed that BA expressed high levels of the mechanosensitive ion channel Piezo1, resulting in a strong Piezo1 current. Treatment of a BA cell line with the β3-adrenergic receptor agonist CL316,243 (CL) increased Piezo1 expression. This effect was dependent on lipolysis activation, as it was blunted by pharmacological inhibition of the triglyceride lipases ATGL and HSL. Activation of the sympathetic nerves in cold-adapted mice also increased Piezo1 expression in BAT and invalidation of both ATGL and HSL in BA significantly reduced Piezo1 induction by cold. We used mice with a specific invalidation of Piezo1 in BA (Piezo1BAd.KO mice) to investigate the role of Piezo1 in BA functions. As expected, Piezo1 expression was markedly reduced in BAT of Piezo1 BAd.KO mice and Piezo1 current was undetectable in isolated BA. On a chow diet, Piezo1 BAd.KO mice had less fat mass than Piezo1fl/fl mice. This reduction was also observed on a high fat diet (HFD) but only during the first 4 weeks of HFD. However, after 13 weeks of HFD, although Piezo1 BAd.KO and Piezo1fl/fl mice had similar fat mass, the glucose tolerance of Piezo1 BAd.KO mice was improved indicating an improved glucose homeostasis. We then treated lean mice of both genotypes with CL for 7 days to investigate the effect of Piezo1 invalidation on BAT activation. Piezo1 deletion in BA did not alter the induction of thermogenic genes including Ucp1 but led to an increased induction of several genes controlling de novo lipogenesis (synthesis of fatty acids from glucose), which optimizes fuel storage and thermogenesis. Our results demonstrate that lipolysis drives Piezo1 expression in BA, which negatively regulates de novo lipogenesis and may affect coupling between lipid metabolism and thermogenesis.

Presentation 2: Océane Bouvet

Role of collagen receptors DDR1/2 in metabolic adaptation of dedifferentiated melanoma cells to extracellular mechanical signals

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Keywords : Melanoma, therapeutic resistance, microenvironment, metabolism, DDR

Despite successful therapies targeting the BRAF oncogenic pathway of melanoma cells or immune checkpoints, resistances and metastatic relapse occur. Adaptive plasticity induced by the microenvironment and therapeutic pressures are described as drivers of therapy resistance (Rambow et al. Genes Dev. 2019). Our team has demonstrated a process of biomechanical adaptation of melanoma to targeted therapies that favors the deposition of extracellular matrix (ECM) components such as collagen, tumor stiffening and therapeutic escape, and identified DDR1/2 collagen receptors in the protection conferred by stromal cell-derived ECM (Girard et al. Cancer Res 2020; Diazzi et al. EMBO Mol Med 2022; Berestjuk et al. EMBO Mol Med 2022). Here, we have investigating DDR's role in melanoma mechanical plasticity using cell culture models on collagen matrices of controlled rigidity combined with 'omics' approaches and using electron and fluorescent microscopy. We found that collagen stiffness promotes proliferation, invasion and drug resistance through DDR, which activate YAP and NFkB pathways on dedifferentiated melanoma cells. DDR also mediate metabolic adaptation in response to mechanical signals by modulating mitochondrial dynamics of melanoma cells and their lipid storage capacities. Metabolomic analyses revealed the activation of the mitochondrial β-oxidation and carnitine biosynthesis pathways by stiff collagen matrices. Finally, we found that the fatty acid degradation pathway induced by mechanical signals correlated with the loss of perilipin-2, a lipid droplet surface protein. Together, these findings provide an original link between ECM signaling, collagen receptors DDRs and melanoma cell metabolism and improve our understanding on the extracellular biomechanical signals that affect tumor cell plasticity and therapeutic adaptation.

POSTERS

Wine and Cheese Poster Session

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1	Chafik	Abderrahman	Axis 3: Stress Signaling	Control of mitochondrial functions by endosomal GTPase Rab4b-dependent mechanisms
2	Clary	Raphaelle	Axis 3: Stress Signaling	Implication of REDD1 in the regulation of cGAS/STING pathway
3	Crusset	Floricia	Axis 4: Signaling in aging and disease progression	Development of a pathophysiological human adipose tissue model of obesity
4	Dussutour	Ange	Axis 5: New principles in signaling and applications	Cross-kingdom RNAi in plant-rootknot nematode
5	Fraissard	Keren	Axis 2: Plasticity and Signaling	Microtubules' glutamylation and resistance to paclitaxel in breast cancer
6	Fytili	Eirini Maria	Axis 2: Plasticity and Signaling	Investigating the role of UBTD1 in gland formation and signaling
7	Gimond	Clotilde	Axis 2: Plasticity and Signaling	C. elegans as a model system to study genetic susceptibility in alcohol-linked cancer
8	Grimanelli	Zoé	Axis 1: Cellular Architecture of Signaling Pathways	Dissecting atomistic, molecular and functional differences between ER receptors VAP A and VAP-B
9	Hofmaenner	Kai	Axis 2: Plasticity and Signaling	Initiating regeneration: Insights from genes with regeneration-specific expression dynamics
10	Jayousi	Faisal	Axis 5: New principles in signaling and applications	Detection and Characterisation of Fibronectin Structures in the Tumour Extracellular Matrix
11	Kostareli	Maria Myrto	Axis 3: Stress Signaling	DIX domains in filamentous plant pathogens: What for?
12	Krawczyk	Ines	Axis 3: Stress Signaling	A Hydrogel Mold to Study Circadian Oscillations in 3D Hepatic Cells
13	Le Parc	Amélie	Axis 3: Stress Signaling	RNA granule formation in Caenorhabditis elegans: roles of environmental stress and effects on fertility
14	Leray	Chloe	Axis 4: Signaling in aging and disease progression	Alteration of maternal RNA stores during oocyte aging
15	Lubrano Di Scampamorte	Hélène	Axis 2: Plasticity and Signaling	Molecular and functional study of the modulation of ASICs by endogenous lipids
16	Mamjoud	Iman	Axis 4: Signaling in aging and disease progression	The adipocyte anti-oncogene p19ARF is involved in the development of obesity and its metabolic complications
17	Mignerot	Laure	Axis 2: Plasticity and Signaling	Behavioral Evolution and environmental plasticity in Caenorhabditis Egg Laying
18	Mousset	Alexandra	Axis 4: Signaling in aging and disease progression	Neutrophil Extracellular Traps (NETs) promote cutaneous Squamous Cell Carcinoma (cSCC) initiation and progression.
19	Nicolini	Victoria	Axis 2: Plasticity and Signaling	Glucocorticoid receptor activation impacts cytoplasmic Processing-body assembly
20	Pierantoni	Alessandra	Axis 4: Signaling in aging and disease progression	From Oocyte to Adult Phenotype: Understanding Intergenerational Programming to Improve Cancer Diagnosis and Treatment
21	Pignol	Marie	Axis 2: Plasticity and Signaling	Preconceptional paternal nutrition influences behavior in offspring
22	Pluis	Max	Axis 3: Stress Signaling	How does Phytophthora make the cut?
23	Popkova	Anna	Axis 1: Cellular Architecture of Signaling Pathways	Studying the mechanism governing pole cell formation: a cross-talk between genetics and mechanics.
24	Rachedi	Nesrine Safi	Axis 4: Signaling in aging and disease progression	Dietary intake and glutamine-serine metabolism control pathologic vascular stiffness.
25	Richter	Margaux	Axis 5: New principles in signaling and applications	Behavioural characterisation of a mouse model lacking the gene coding for augurin, a novel negative modulator of the canonical Wnt signalling pathway
26	Strazzulla	Axelle	Axis 4: Signaling in aging and disease progression	CD44 could aggravate liver fibrosis by regulating hepatic stellate cell functions
27	Tanari	Abdul Basith	Axis 1: Cellular Architecture of Signaling Pathways	Mechanics and mechanisms driving epithelial folding during gastrulation
28	Techer	Hervé	Axis 3: Stress Signaling	MRE11 and TREX1 control senescence by coordinating replication stress and interferon signaling
29	Vayankara Edachola	Sreeparvathy	Axis 3: Stress Signaling	Plasticity and composition of stress-induced RNA condensates
30	Vu	To Giang	Axis 4: Signaling in aging and disease progression	Lack of MDA5 delays HSC aging partly by retaining proteostasis
31	Wurtz	Mickael	Axis 4: Signaling in aging and disease progression	Regeneration as a tool to study the longevity in the sea anemone Nematostella vectensis
32	Zhu	Xiaoxuan	Axis 3: Stress Signaling	Role of FERONIA during Plant-Oomycete interactions: trojan horse or true defender?

1 - Chafik Abderrahman – Axis 3

Control of mitochondrial functions by endosomal GTPase Rab4b-dependent mechanisms

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Keywords : Mitochondria, Rab4b, T-cells, Metabolism, Endocytosis

There is increasing evidence about the involvement of endocytosis and its players in the control of mitochondrial function. Here we show that the endosomal small GTPase Rab4b is required for proper mitochondrial activity in T cells. We found that the knockout of Rab4b in T cells reduced mitochondrial membrane potential and mitochondrial respiration, leading to reduced ATP production. This reduced mitochondrial activity was not due to an increased oxidative stress, apoptosis or mitophagy. There were also no major changes in the transcriptional program, mitochondrial morphology and localization. Interestingly, we found that some Rab4b-positive vesicles partially colocalized with mitochondria and that Rab4b deficiency in T cells resulted in reduced iron transfer to mitochondria. These data support the hypothesis that Rab4b may control iron transfer from endosomes to mitochondria by linking the two organelles, which would affect mitochondrial metabolism.

2 - Clary Raphaelle – Axis 3

Implication of REDD1 in the regulation of cGAS/STING pathway

Raphaëlle Clary, Karine Dumas, Jérôme Gilleron, Jennifer Jager, Inès Mucel, Brice Angot, Mireille Cormont, Jean-François Tanti and Sophie Giorgetti-Peraldi

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Keywords : Obesity ; Mitochondria ; Oxidative stress ; REDD1 ; cGAS-STING

Obesity is characterized by the expansion of adipose tissue (AT). It is a major public health issue due to its comorbidities, such as type 2 diabetes, liver diseases, cardiovascular diseases and cancer. Expansion of AT leads to its dysfunction with the development of inflammation, hypoxia, oxidative stress, and mitochondrial dysfunction. Mitochondrial dysfunction within the AT participates in the development of insulin resistance by few mechanisms, among others, (i) the generation of oxidative stress and (ii) the activation of Serine / Threonine Kinases that inhibit the insulin pathway. Mitochondrial dysfunction also leads to the activation of the inflammatory pathway cGAS/STING described to recognize cytosolic dsDNA. Moreover, literature has shown that the cGAS/STING pathway is upregulated in the AT of obese mice. In our team, we investigate molecular mechanisms behind the AT dysfunction, and we identified the stress response protein REDD1 (Regulated in Development and DNA Damage responses-1), a mTORC1 inhibitor, as one of the possible actors of insulin resistance in the AT of obese mice. In this work we investigate whether REDD1 is involved in the regulation of the cGAS/STING pathway. Downregulation of REDD1 expression in 3T3-L1 adipocytes with siRNA (siREDD1 adipocytes) leads to (i) an upregulation of the expression of oxidative stress markers such as NRF2 and the phosphorylation of p38 MAPK and (ii) an increase of the expression of cGAS, STING and the phosphorylation of TBK1 (substrate of the cGAS/STING pathway). To determine if the mechanisms behind the regulation of cGAS and STING by REDD1 are (i) dependent on mTORC1 signaling pathway and oxidative stress, we used rapamycin (known mTORC1 inhibitor) and N-Acetyl Cysteine (an antioxidant). Both those treatments showed a decrease in the expression of cGAS and STING compared to the untreated siREDD1 adipocytes suggesting that the regulation of the expression of cGAS and STING by REDD1 depends on both mTORC1 and oxidative stress. We correlated those observations with an In vivo heterozygous mouse model for REDD1 (REDD1+/- mice). REDD1+/- mice were insulin resistant and displayed increased oxidative stress markers (NRF2 and P-p38MAPK) and cGAS and STING compared to wild-type mice. This work suggests that REDD1 regulates the cGAS/STING pathway, and it appears that the mechanism is mTORC1 and ROS-dependent. The link between REDD1, mitochondrial dysfunction and cGAS/STING pathway is still under investigation.

3 - Crusset Floricia – Axis 4

Development of a pathophysiological human adipose tissue model of obesity

Crusset.F; Lecorgne.E; Fassy.J; Iannelli.A; Chignon-Sicard.B; Ben Amor.I; Formicola.L; Doglio.A; Dani.C; Mari.B; Vassaux.G; Dani.V

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Keywords: Adipose tissue, Obesity, inflammation, fibrosis, 3D model

Development of obesity leads to remodelling of adipose tissue and low-grade inflammation. This results in modifications in vascularisation, infiltration of immune cells and changes in organisation of extracellular matrix leading to fibrosis. As the storage capacity of adipocytes is affected, ectopic accumulation of triglycerides in other organs favours the development of insulin resistance, inflammation and fibrosis in peripheral tissues, leading to metabolic diseases such as type 2 diabetes, MASH (Metabolic Asssociated Steatolic liver disease) and cardiovascular disease. New clinically relevant models are needed to screen a large number of pharmaceutical molecules and provide a better understanding of the pathophysiology of obesity and related metabolic disorders. ExAdEx-Innov established a novel 3D adipose tissue model, named ExAdEx, that can be generated from AT biopsy material of different origins, including subcutaneous AT from donors without obesity (i.e. aesthetic surgery waste). This process allows to maintain adipose tissue 3D structure, microenvironment, adipocyte stem cells populations, vascular and lymphatic networks and extra-cellular matrix. Exadex model remains functional and retains all its characteristics and physiological responses throughout 8 weeks of culture. A key objective of ExAdEx-Innov is to develop a physio-pathological model of obese adipose tissue based on the ExAdEx model derived from adipose tissue from donors without obesity. However, the expression levels of inflammatory and fibrotic markers in humans with obesity are not yet well characterised in the literature. We are currently establishing a molecular, phenotypic and functional profile of adipose tissue from obese patients. A qPCR device using microfluidics enabling us to screen genes at medium throughput and a tool allowing the simultaneous assay of around ten inflammatory cytokines have been used. Then, the aim is to produce a model of physio-pathological adipose tissue with a similar signature to obese visceral adipose tissue, owing to its association with various metabolic diseases. On the functional level, the results show a specific inflammatory profile of visceral obese adipose tissue, compared with subcutaneous obese tissue. Based on preliminary results, it also appears that a certain kinetics of stimulation of lean adipose tissue with TNFα induces an inflammatory response similar to the one observed in obese visceral adipose tissue. At the molecular level, we identify modulation of genes involved in the mechanism of fibrosis in obese visceral and subcutaneous tissues compared to lean adipose tissue. In addition, we are also able to modulate these genes in ExAdEx model using different stimuli, which could enable us to produce a model of fibrotic adipose tissue close to the physiopathological visceral adipose tissue.

4 - Dussutour Ange – Axis 5

Cross-kingdom RNAi in plant-rootknot nematode

Ange Dussutour, Martine Da-Rocha, Yara Noureddine, Karine Mulet, Claire Caravel, Pauline Foubert, An-Po Cheng, Jérome Zervudacki, Arne Weiberg, Lionel Navarro, Bruno Favery, Stéphanie Jaubert

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Keywords : Cross-kingdom RNAi, RNA interference, small non-coding RNA, Meloidogyne incognita, Solanum lycopersicum

Transkingdom and inter-organism silencing refers to a new pathway of molecular dialogue in parasitic interactions. This process consists of the exchange of non-coding RNAs (ncRNAs) between two organisms that may belong to different kingdoms. This process has been identified in the interaction between the vertebrate parasitic nematode Heligmosomoides polygyrus and the mouse (Buck et al. 2014) or between the fungus Botrytis cinerea and the model plant Arabidopsis thaliana (Weiberg et al. 2013). In both cases, pathogens were shown to secrete ncRNAs into host tissues to silence host genes involved in the immune response. Since then, only a few articles have highlighted the key role of ncRNA exchange in host-parasite interactions. Nematodes of the genus Meloidogyne are among the most important agricultural pests. To date, no study has been conducted to characterise the exchange of ncRNAs during plant-nematode interactions. The aim of this PhD project is to determine whether RKN secrete ncRNAs into root cells and to characterise the role of inter-organism silencing in plant-nematode interaction. Initial sequencing analyses have identified several candidates: nematode small ncRNAs and their target plant messenger transcript. Direct identification and functional analyses are needed to validate and elucidate the role of the identified nematode small ncRNA/plant mRNA pairs in plant-nematode interactions. This project will open new perspectives in the study of host-parasite dialogue and the development of new pest management strategies.

5 - Fraissard Keren– Axis 2

Microtubules' glutamylation and resistance to paclitaxel in breast cancer

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Keywords : glutamylation, breast cancer, resistance, paclitaxel, microtubules

Context: Breast cancer is the most frequent cancer in women worldwide. Triple negative breast cancer represents 20% of breast cancers and is a sub-type in which cells do not have the hormonal receptors, preventing them from being sensitive to common treatments (Yin et al., Brest Cancer Res, 2021). The main mode of treatment for triple negative breast cancer is surgery coupled with chemotherapy. A common chemotherapy treatment is paclitaxel, it has been used for thirty years (Orr et all, Oncogene, 2003). Paclitaxel is efficient for short-term treatment, but in the long run cells become resistant (Łukasiewicz et al., Cancers, 2020). Paclitaxel stabilizes microtubules which prevent cells from dividing (Orr et all, Oncogene, 2003). It has been showed that microtubules' glutamylation stabilises microtubules' network in breast cancer cells (Torrino et al., Cell metabolism, 2021). Because paclitaxel and microtubules' glutamylation both stabilize breast cancer cells' microtubules, we hypothesize that microtubules' glutamylation could be part of the paclitaxel resistance mechanism in breast cancer cells. Objectives: Creating paclitaxel resistant cell lines and characterizing them to determine whether and how microtubules' glutamylation is involved in resistance to paclitaxel. Results: I work with two triple negative breast cancer cell lines, MDA-MB-231 and MDA-MB-468. First of all, I carried out tests to determine the effect of paclitaxel on these two cell lines. I established the non-lethal dose to administer to MDA-MB-231 and MDA-MB-468 in order to make them resistant to paclitaxel. I then created different resistant cell lines non-simultaneously in order to obtain different types of mutations leading to resistance to paclitaxel. I obtained one resistant cell line of MDA-MB-231 and one resistant cell line of MDA-MB-468. I performed western blots to evaluate the level of microtubule glutamylation in resistant and sensitive cells of each line. In these cell lines, microtubule glutamylation is increased in resistant cells compared to paclitaxel-sensitive cells. I therefore began to characterize the migration and invasion of these cells using 2D wound healing and invasion experiments in 3D spheroids. I also began to characterize the shape of the microtubule network of resistant cells by immunofluorescence. Future work: I am now completing this work and studying the proliferation and apoptosis of resistant cells by Ki67 and cleaved Caspase 3 stainings. Later on, I will use a microtubule glutamylation mutant on my resistant cells to see if this restores the phenotype, particularly for invasion and migration.

6 - Fytili Eirini Maria– Axis 2

Investigating the role of UBTD1 in gland formation and signaling

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Keywords : UBTD1 , Glands , palmitoylation , myristoylation, post translational modifications

Glands are organs that produce and secrete substances that have important role in our body. Mammary glands are responsible for milk secretion for breastfeeding of the offspring and prostate is important for the secretion of seminal liquid .The epithelium of both glands is formed by a bilayer of cells, luminal cells that have secretory properties ,surrounded by basal cells that provide a structural support for the epithelium and maintain the ductal integrity .The architecture of glands is crucial for their function and maintenance , which relies on the fine balance of proliferation and differentiation controlled by adult stem cells. Stem cells behavior is controlled by chemical and mechanical signals coming from their surrounding environment. We previously identified UBTD1 as a mechanoregulator that controls a major mechanotransduction pathway YAP. In addition, we demonstrated that UBTD1 is crucial to regulate the EGF signaling. This signaling pathway is important for epithelial maintenance, stem cells and cancer. Since UBTD1 is expressed in basal stem cells in gland, our objective is to decipher the role of UBTD1 in gland formation and maintenance. Towards this goal we followed a structural approach and studied the localisation of the protein and by in silico structural analysis analysis we identified two potential acylation sites on the N-terminal of the protein. We showed that UBTD1 is palmitoylated and myristoylated and that because of this dual acylation UBTD1 is located at the plasma membrane and because of this dual acylation UBTD1 is located at the plasma membrane. By studying the half-life and the trafficking of the protein in the cell, we proved that palmitoylation is responsible for UBTD1 localization and stability at the membrane. We used a proteomic approach to identify potential partners. Finally, at a cellular level, preliminary data of the team showed that when we overexpress UBTD1 there is a defect in cell matrix adhesion. We studied adhesion upon knock down of UBTD1 and quantified intracellular and extracellular fibronectin secretion. We showed that UBTD1 controls fibronectin secretion and that TGFbeta regulates UBTD1.In perspective we are planning to study some aspects of the glands such as secretion and proliferation in 3D models of organoids.

7 - Gimond Clotilde– Axis 2

C. elegans as a model system to study genetic susceptibility in alcohol-linked cancer

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Keywords : C. elegans, cancer, alcohol, genetic polymorphisms

Numerous epidemiological studies have suggested an association between the risk of developing alcohol-related cancers and certain genetic polymorphisms carried by genes coding for enzymes involved in alcohol metabolism and molecular players involved in drinking habits. While these data suggest the importance of taking them into account in prevention programs and personalized medicine, the causal value of these polymorphisms in the metabolic and behavioral stages that promote cancer is difficult to establish with certainty in humans. We propose to transpose the validation of previously described polymorphisms and the identification of new alcohol-relevant variants to the nematode C. elegans, a model organism for which we have more than 500 genetically distinct wild strains, characterized by unique combinations of allelic variants. Our project will combine genetics, bioinformatics and behavioral approaches: 1) The responses of wild strains to alcohol will be compared in two very simple behavioral tests: firstly, locomotion, which is affected by alcohol in a similar way in worms and humans, and in which the genes involved are common to both species. Egg laying will also be tested, as it relies on a very simple neuro-muscular network, operating via multiple signaling elements (neurotransmitters, receptors, ion channels), which the literature has shown to be targets of alcohol in humans. Our preliminary results on a subset of strains showed that egg-laying response to alcohol is genotype-dependent. 2) Subsequently, these phenotypic data will be used to identify the genetic polymorphisms responsible for inter-strain differences in responses to alcohol, by GWAS analysis, commonly used in oncology, and other quantitative genetic methods. 3) We will also develop a complementary axis, in which we will introduce human candidate variants into the corresponding sequence in worm orthologs by CRISPR-Cas9 gene editing, to address their effects on alcohol-induced worm behavior. We expect to find and validate multiple genetic variants influencing the metabolism of alcohol by conversion enzymes, as well as other polymorphisms carried by genes linked to neuromuscular function. Our results should enable the development of tools to be used in preventive settings and follow-up actions. Finally, this project will also have potentially significant benefits within a broader cancerology context: the discovery of genetic polymorphisms that modify the activity of detoxification enzymes, thus providing a better understanding of their roles in chemoresistance.

8 - Grimanelli Zoé– Axis 1

Dissecting atomistic, molecular and functional differences between ER receptors VAP A and VAP-B

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Keywords : VAP-A, VAP-B, Membrane Contact Site, Endoplasmic Reticulum, Molecular Dynamics Simulations

VAP-A and its paralog VAP-B are conserved dimeric integral type II membrane receptors of the endoplasmic reticulum (ER). They encompass an N-terminal Major Sperm Protein (MSP) domain, a central coiled-coil (CC) region and a C terminal transmembrane domain (TMD), with two linkers (L1, L2) connecting these domains together. Through their MSP, they bind multiple proteins containing an FFAT motif, such as the lipid-transfer protein OSBP. The VAP-OSBP complex allows cholesterol/PI(4)P exchange at ER-Golgi membrane contact site. Although VAP-A and VAP-B share 83% similarity, some functional specificities have been identified. However, little is known about the molecular characteristics that distinguish these two proteins. To explain the maintenance of both proteins during evolution, we used cellular and in silico approaches dissecting each VAP region. By performing rescue experiments on VAP-A KO or VAP-B KO human cells, we identified key features that enable VAP-A, but not VAP-B, to restore OSBP function at contact sites. Our results, obtained using VAP-A/VAP-B chimeras, indicate that the fundamental difference between these two proteins lies in their TMDs. To further assess the role of this region, we performed Molecular Dynamics (MD) simulations of VAP-A and VAP-B TMDs in membranes mimicking the ER with different cholesterol levels. Our results show a higher stability of the VAP-B TMD dimer, with an increased sensitivity for cholesterol for VAP-A. We hypothesize that the local lipid environment is sensed differently by VAP-A or VAP-B TMDs, thus contributing to the differences in distribution and function of VAP-A and VAP-B.

9 - Hofmaenner Kai– Axis 2

Initiating regeneration: Insights from genes with regeneration-specific expression dynamics

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Keywords : Development, Regeneration, plasticity, Wnt activation

To what extent regeneration redeploys the molecular mechanisms underlying embryogenesis is a historical question in the field of regeneration biology. Using the sea anemone Nematostella vectensis (Cnidaria, Anthozoa),, a recent study performed a comparative transcriptome analysis and revealed a set of genes with a regeneration-specific expression dynamics . To decipher the role these genes may play during regeneration in N. vectensis, the current project is articulated around three specific axes: 1) Selection and characterization of the spatio-temporal expression dynamics of the “regeneration- specific” genes of interest (rsGOIs) using temporal expression data and whole mount in situ hybridization; 2) Identification of regulatory elements initiating injury-induced “regeneration-specific” gene expression using ATAC-seq and cis- regulatory assays; 3) Investigation of the role (requirement / sufficiency) of the rsGOIs using functional genomic approaches (KO/KI). We have determined a list of 23 rsGOIs whose expression is activated shortly after injury (2-4hpa) and at the onset of regeneration (18-24hpa). Their expression is restricted at the amputation-site and /or in the mesenteries, an internal structure that is crucially required for the initiation of the process of regeneration. The development of constitutive KO lines, as well as a conditional overexpression system to test the sufficiency of the rsGOIs have been initiated. To develop relevant “sufficiency” assays, we have performed an in-depth analysis of the capacity of cWnt activation to initiate ectopic head formation following injury. This allowed us to understand the duration during which the injury is permissive for a pro- regenerative response. In sum, this works sets the foundation to assess and understand the roles of rsGOIs at the onset of regeneration and their potential sufficiency to induce a regenerative response.

10 - Jayousi Faisal– Axis 5

Detection and Characterisation of Fibronectin Structures in the Tumour Extracellular Matrix

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Keywords : extracellular matrix, tessellations, fluorescence microscopy, bioimage analysis, circular statistics

Characterising the tumour extracellular matrix (ECM) holds promise for identifying predictive biomarkers, particularly in assessing patient response to immunotherapy. While the cellular components of the tumour microenvironment have been extensively characterised, the non-cellular elements of this ecosystem remain underexplored. In this study, we investigated the geometry of Fibronectin (FN) in immunofluorescence images, a key ECM protein, in head and neck tumours. Our analysis identified two primary classes associated with FN structure: (a) aligned fibres, and (b) reticular fibre-like, which exist on a spectrum of structural variation. We proposed an approach leveraging Voronoi diagrams as adaptive windows. Circular statistics were then used to capture the spatial organisation of FN, providing insights into its structural heterogeneity within the tumour microenvironment.

11 - Kostareli Maria Myrto – Axis 3

DIX domains in filamentous plant pathogens: What for?

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Keywords : DIX domains, polarity, filamentous pathogens, oomycetes, pathogen development

Cell polarity is a fundamental process in living organisms, critical for development and cellular organization. In animals, cell polarity is primarily regulated by the Wnt/β-catenin signaling pathway, where DIX (DIshevelled and aXin) domain-containing proteins (DDPs) have a pivotal role in protein aggregation. Interestingly, oomycetes, a group of filamentous plant pathogens, closely related to malaria parasites, also contain DDPs, unlike fungi. Oomycetes lack the Wnt/β-catenin signaling pathway, raising questions about the role of DDPs in these organisms. Oomycete DDPs form unique domain combinations (e.g., DnaJ, kinase and ELMO domains), suggesting genetic innovations that could lead to distinct biological functions. My PhD project aims to decipher the role of oomycete DDPs. Preliminary data indicate that these proteins interact with cytoskeletal proteins and possibly participate in vesicle trafficking and cellular signaling, mechanisms involved in polar growth. Understanding their functions will provide valuable insights into the specificities of oomycete biology and the molecular mechanisms driving pathogen development.

12 - Krawczyk Ines– Axis 3

A Hydrogel Mold to Study Circadian Oscillations in 3D Hepatic Cells

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Keywords : Circadian clock, Hepatocyte, Hydrogel, Silicone mold, Spheroids

Most physiological and behavioral processes, including metabolism, endocrine and immune functions, exhibit circadian (~24 h) rhythms synchronized with the light/dark cycle. In mammals, these oscillations are governed by an internal molecular clock present in almost every cell. Cellular circadian clocks are classically investigated in vitro using two-dimensional (2D) cell cultures despite numerous limitations, such as the disturbance of intercellular interactions, loss of polarity, substrate stiffness, dedifferentiation. Although three-dimensional model systems (3D) address these issues, there use in chronobiology studies remain very limited. We have designed a method consisting of a 3D printed resin mold (+ mold) from with which a reusable, autoclavable silicone mold (- mold) is produced and used to obtain an agarose hydrogel with multiple microwells. Using a non-tumoral mouse hepatocyte cell line we produced spheroids of desired sized with significantly increased expression of hepatic differentiation markers. By combing our technology with real-time luminometry, we show hepatocyte spheroids containing a clock reporter display circadian oscillation for up to 7 days. This approach will enable us to explore circadian clock function in vitro under more physiological conditions and address with potential applications in pharmacology and toxicology.

RNA granule formation in Caenorhabditis elegans: roles of environmental stress and effects on fertility

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Keywords : Caenorhabditis elegans, RNA granule, oogenic germline, environnement, CRISPR

Diverse organisms exhibit many types of RNA granules, condensates composed of RNA-binding proteins and repressed RNAs, however, their functions are still poorly understood. We study the effects of the environment on RNA granule formation in the oogenic germline of the nematode Caenorhabditis elegans. We started to quantify RNA granule formation in various environments using a novel CRISPR-engineered strain containing fluorescent reporters that distinguish two granule types, P-bodies (PUF-5) and stress granules (GTBP-1). We found heat shock (32°C), cold exposure (6°C) and osmotic stress (500mM NaCl) to consistently induce germline granules. Importantly, however, their characteristics (presence, number, size and localization) can vary between the three environmental stresses. To study the possible function of such stress-induced granules and their impact on oocyte viability, we used RNAi to prevent P-body formation. While the three stresses have no or weak effects oocyte viability in control animals, RNAi treatment significantly reduced oocyte viability in both temperature extremes (but not in osmotic stress). Together, these results indicate that the process of RNA granule formation in the C. elegans germline can be stress-specific and likely contributes to protecting oocytes against environmental stress. Now, using these established experimental methods, we aim to characterize the molecular basis of differences in stress-induced RNA-granule formation across natural C. elegans strains.

14 - Leray Chloe – Axis 4

Alteration of maternal RNA stores during oocyte aging

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Keywords: Aging,P-Bodies,C.Elegans,fertility,mRNA storage

RNA aggregation is a hallmark of degenerative cells, but RNAs can also super-assemble into non-pathological condensates, that are indicative of a healthy cellular response to stress or quiescence (Cardona et al., 2023). The debate persists on whether condensation, initially a protective mechanism, becomes pathological during aging. While the time-dependent maturation of RNA condensates is well-documented in vitro, the aging of RNA condensates in animal models remains unexplored. To investigate the impact of aging on RNA condensates, we use C. elegans oocytes as a model, with a focus on the prolonged storage of maternal mRNAs within P-bodies. As expected, and confirming the relevance of our model, aging is linked to reduced fertility, and decreased embryonic viability. More interestingly, using imaging approaches, I demonstrated that the loss of maternal mRNA condensates sphericity, and a dramatic size reduction of these maternal stores, correlated with a surge in embryonic lethality. The loss of sphericity is reminiscent of the solidification of semi-liquid condensates into pathological aggregates, a signature of degenerative cells. The drop in condensate size further suggest a progressive decay of maternal mRNA across aging. Furthermore, for animal of similar age, the condensate size was a strong predictor of embryonic lethality, suggesting that the size of the maternal mRNA store could be a crucial determinant of oocyte fitness. I also observed an age dependent depletion of proteins that are essential for RNA condensate assembly, suggesting a possible molecular mechanism for the age dependant disruption of maternal P-bodies. Our current objective is to further comprehend the compositional alterations of oocyte P-Bodies during the aging process and their consequences on embryonic viability. To achieve this goal, I purified the subcellular oocyte P-bodies using a cutting edge FAPS purification method that has been developped in our lab. The method relies on our ability to separate subcellular particles depending on their size and fluorescence. I controlled the RNA integrity before sending the corresponding RNA for sequencing to identify compositional changes in RNA condensates during aging. In parallel, mRNA translation alterations during aging will be studied through polysome profiling. Using an animal model, my research will provide a better understanding of the impact of physiological aging on the structure and composition of mRNA condensates, and will further test the consequences in maternal RNA expression deregulation and fertility loss.

15 - Lubrano Di Scampamorte Hélène – Axis 2

Molecular and functional study of the modulation of ASICs by endogenous lipids

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Keywords : Ion Channels, Pain Pathway, Lipids, ASICs

ASICs are excitatory cationic channels known to be activated by extracellular protons. They are widely expressed in the entire pathway of pain, where they appear as emerging actors in the signalling pathways of nociception and pain. Moreover, besides protons, we identified endogenous lipids – such as lyso-phosphatidylcholine (LPC) – as new modulators of ASICs. These lipids are therefore able to alter nociceptive signalling with pathophysiological consequences for the development of rheumatic pain. Here, we investigated the effects of LPC analogues on ASIC3, identifying some of them as potentiators and/or activators of ASIC3. Their effects were similar to that of the LPC and dependent on extracellular pH. This investigation aims to better characterise the molecular mechanisms by which lipids act on ASIC3, with perspectives towards a better understanding of nociception signalling, through ASIC3, involved in rheumatic pain pathophysiology.

16 - Mamjoud Iman – Axis 4

The adipocyte anti-oncogene p19ARF is involved in the development of obesity and its metabolic complications

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Keywords: Obesity, Diabetes, Adipocytes, p19ARF, Metabolism

Obesity is on the rise worldwide and is a major risk factor for serious diet-related noncommunicable diseases, including type 2 diabetes, cardiovascular disease, liver disease, and certain cancers. Obesity is characterized by the expansion of adipose tissue, which progressively loses its metabolic and endocrine functions required for glucolipid homeostasis. The establishment of oxidative and inflammatory stress in adipose tissue is implicated in the development of the metabolic complications of obesity. Adipose tissue stress response pathways are largely responsible. These pathways include the DNA damage response pathway, which, when chronically activated, can lead to an increase in senescence markers such as the anti-oncogene p19ARF. P19ARF serves as an anti-oncogene and its best known function is to stabilize the oncogenic transcription factor p53. We have previously shown that p19ARF expression in adipocytes increases very early after initiation of a high fat diet in mice. Therefore, we aimed to decipher the consequences of this overexpression for the development of obesity and its associated complications. To achieve our goal, we generated mice with p19ARF deleted in white and beige/brown adipocytes, by crossing p19ARF fl/fl mice with AdipoQ-Cre mice (p19ARF AdKO). P19ARF AdKO mice had no metabolic phenotype when fed normal chow. When fed a high-fat diet, p19ARF AdKO mice became glucose intolerant and insulin resistant. Transcriptome analysis revealed an increased enrichment of inflammation, fibrosis, and metabolic pathways in p19ARF AdKO mice compared to controls. These complications may arise because p19ARF AdKO mice gain more weight and fat mass than their control littermates, despite eating the same and engaging in the same activity. However, the energy expenditure of p19ARF AdKO mice is lower than that of control mice, which may explain why they are more prone to obesity. This suggests that the thermogenic activity of the brown adipose tissue is defective in p19ARF AdKO mice. Consistent with this, p19ARF AdKO mice in thermoneutrality, where the brown adipose tissue is inactive, have the same metabolic phenotype as their control littermates. However, the knockout of p19ARF only in the brown adipose tissue did not affect body weight gain and glucolipid metabolism. Thus, knockout of p19ARF in white adipocytes is responsible for the increased weight gain in p19ARF AdKO mice. Since the best described role of p19ARF is to destabilize p53, we studied mice knocked out for p53 in adipocytes. We found that these mice do not develop obesity and metabolic complications under the same experimental conditions. Thus, the effect of p19ARF knockout in adipocytes does not require p53. In conclusion, the increased expression of p19ARF at the onset of obesity may serve as a protective mechanism against obesity and its associated complications. We now need to identify the p19ARF-dependent mechanism in adipocytes involved in this protective effect.

17 - Mignerot Laure – Axis 2

Behavioral Evolution and environmental plasticity in Caenorhabditis Egg Laying

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Keywords: Egg-laying circuit, nematode, plasticity, Quantitative Trait Loci, behaviour

C. elegans egg-laying behaviour underlies a structurally simple neural circuit, which has served as an important model in neurogenetics. Here we present our ongoing characterization of natural divergence in the nematode egg-laying circuit, ultimately aimed at identifying the neural and molecular determinants that generate variation in this central reproductive behaviour. Analysing ~40 Caenorhabditis species and hundreds of wild isolates, we show that the nematode egg-laying circuit exhibits complex evolutionary variability, not only among populations within C. elegans but also among different Caenorhabditis species. Egg-laying activity is also strongly modulated by environmental stimuli, but species and isolates may respond vary differently to the same stimulus, underscoring the presence of genotype-by-environment interactions (GEI) in egg-laying behavior. For our forthcoming Signalife presentation, we will specifically focus on recent results that seek to elucidate the genetic underpinnings of such GEI in egg-laying activity, employing Quantitative Trait Locus (QTL) mapping in C. elegans as our primary investigative tool.

18 - Mousset Alexandra- Axis 4

Neutrophil Extracellular Traps (NETs) promote cutaneous Squamous Cell Carcinoma (cSCC) initiation and progression.

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Keywords: Cancer, initiation, inflammation, neutrophil, NETs

Inflammation is an immune system response to infection aimed at eliminating harmful stimuli and initiate tissue repair. However, chronic inflammation is known to predispose to cancer development and conversely, cancer cells can trigger inflammation to promote cancer progression. While neutrophils are the largest portion of leukocytes and are among the first cells recruited to the inflammatory site, their role in cancer has only recently been studied. A specific neutrophil function is the release of Neutrophil Extracellular Traps (NETs). NETs are DNA strands decorated with enzymes and proteins and released in the extracellular space to trap and kill pathogens. Recently, we have shown that NETs have pro-tumoral activities such as their involvement in metastatic cells chemoresistance, however their role in cancer initiation is still unknow. To study NETs specifically in cancer initiation, we use an established mouse model of skin squamous cell carcinoma (SCC) chemically induced by the application on mice skin of carcinogen DMBA, and cancer promotor TPA. We show that targeting NETs either at early stage of carcinogenesis or during tumor progression, counteract SCC initiation and progression. More specifically, we demonstrate that NETs amplify DNA damage accumulation in skin cells. Subsequently, more oncogenic mutation can occur, leading cancer cell onset. Overall, our work aims to uncover all roles of NETs in SCC carcinogenesis to identify new therapeutic target and to develop new ways of improving the prevention, treatment, and survival of cancer patients.

19 - Nicolini Victoria– Axis 2

Glucocorticoid receptor activation impacts cytoplasmic Processing-body assembly

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Keywords : glucocorticoid receptor, glucocorticoid, processing-bodies

Processing-bodies (P-bodies) are described as small cytoplasmic, membraneless organelles that play an important role in various cellular processes by controlling RNA translation. P-bodies are formed by the coalescence of untranslated mRNA and multiple RNA-binding proteins through liquid-liquid phase separation. Despite recent discoveries about their own key components, the cellular pathways that control their formation are poorly understood. In this context, we performed a drug screen to identify targets that can promote P-body formation. We found that glucocorticoids (GC) can increase the number of P-bodies in cells within 48 hours of treatment in epithelial cells. In addition, we showed, by genetic invalidation, that GR activation is required to increase the number of P-bodies upon GC treatment. Furthermore, we determined that only rescue with the GRa isoform was able to reproduce a change in P-body regulation in an inverted U-shape dose response, suggesting that both GC and GRa levels are important for triggering P-body reshaping. Finally, we evidenced that this phenotype is transient and reverts after GC removal. Overall, our results show that, in addition to its known transcriptional activity, GR is also able to influence global RNA storage and translation in different epithelial cell types.

20 - Pierantoni Alessandra– Axis 4

From Oocyte to Adult Phenotype: Understanding Intergenerational Programming to Improve Cancer Diagnosis and Treatment

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Keywords : p16, senescence, cancer, embryogenesis, cGAS-STING

Cellular senescence is mainly described as a state of permanent cell cycle arrest in response to different stress such as DNA damage-inducing factors as well as with aging. Excessive accumulation of senescent cells can negatively impact different tissues, creating a proinflammatory environment that is permissive for development of various age-related diseases, including cancer. This project is related to the analysis of senescent and senescent-like cells that express a high level of the cell cycle inhibitor gene, p16. Specifically, we found that there is a small but noticeable fraction of mouse oocytes (around 9%) that activate a state of p16, that normally reflects a strong DNA damage or senescence activation, both should be resulting in irreversible cell cycle arrest. This should be incompatible with fertilization of such oocytes and subsequent embryogenesis. In contrast, we found that p16highoocytes could be efficiently fertilized, undergo embryonic development and give rise to visually healthy mice. More in depth analysis, however, revealed that such mice after reaching the adult stage exhibit several abnormalities with most pronounced changed observed in the hematopoietic system. In adulthood, these mice experience a drop in the percentage of various immune cell subsets, resulting in an immune system exhaustion. As a result, in models of tumorigenesis, these mice exhibit reduced sensitivity to cancer treatment and an increased risk of relapse. This project aims to unveil the molecular mechanism(s) behind the epigenetic program activated in p16High oocytes. This program persists across fertilization and remains partially active in adult animals, contributing to lasting phenotypes. Although our focus is on mice, it's important to note the parallels with humans. This, in turn, could influence the approach to cancer treatment for individuals in this category. Identifying this group allows for more precise therapy, with the prospect of reversing certain epigenetic marks imposed by a p16High state during oocyte development..

21 - Pignol Marie– Axis 2

Preconceptional paternal nutrition influences behavior in offspring

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Keywords : Nutritional geometry, paternal effect, epigenetics, behavior development, metabolism

Environmental factors such as physical activity, nutrition and pollutants influence the health of the reproductive system as well as the epigenetic program carried by gametes (oocytes and spermatozoa). Our laboratory and others investigating parental effects have observed sex-specific effects for both metabolic and behavioural traits in the offspring as a result of altered preconceptional paternal diet. However, the mechanisms by which paternal nutrition rewires the developmental programming of the offspring towards an altered behavioural phenotype are unknown. We hypothesize that the protein level rewires the epigenetic make-up of spermatozoa, which in turn modulates the development of the central nervous system in the offspring. To address this hypothesis, male mice were fed on iso-caloric diets with different macronutrient compositions designed by using the nutritional geometry framework. Fathers were mated with female mice fed with standard diet to generate offspring fed with standard diet. In F1 generation, we recorded anhedonia in male offspring of high-protein fathers. Female offspring of low-protein fathers have an exploratory deficit and memory impairment. Interestingly, paternal diet also changes the inflammatory pathways in male offspring. These results confirm that macronutrients imbalance in paternal nutrition, in particular protein level, affects the central nervous system development in offspring. We aim to identify the neuronal pathways impaired and the epigenetic mechanisms responsible for the brain development in offspring.

22 - Pluis Max – Axis 3

How does Phytophthora make the cut?

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Keywords : Phytophthora, mechanosensitive channels, cadherins, appressoria, actin

Filamentous plant pathogens cause significant yield losses in agriculture and forestry. One particularly devastating group, related to malaria parasites, is Phytophthora meaning "plant destroyers". The success of these microbes relies on the formation of specialized structures that help them penetrate and colonize the host's tissues. However, how Phytophthora species recognize the host surface and the signaling cascades that trigger the differentiation of infection structures remain elusive. My PhD project will focus on appressoria, the structures that breach the plant cuticle and cell wall to initiate colonization. Oomycetes use the appressoria like a microscopic knife to slice through the plant surface which requires less turgor pressure compared to other filamentous pathogens. As mechanical stimuli play a central role in the formation of oomycete appressoria, I will identify the mechanosensitive proteins that detect these stimuli. Additionally, I will characterize the signaling cascades that connect these receptors to the actin cytoskeleton to initiate cytoskeleton remodeling, which is responsible for forming the microscopic knife called an actin aster. Ultimately, my research will uncover key aspects of the biomechanics of Phytophthora's infection strategy, paving the way for the development of anti-penetrant molecules and new strategies for plant tissue engineering.

23 - Popkova Anna– Axis 1

Studying the mechanism governing pole cell formation: a cross-talk between genetics and mechanics.

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Keywords : gene patterning , mechanics, pole cell, light sheet microscopy, myosin

Many morphogenetic processes rely on interactions between microtubules, actin and myosin. Cell budding, including the asymmetric division and subsequent release of a daughter cell, is a fundamental process in development and disease. In early Drosophila embryogenesis, rapid cytoskeletal reorganization correlate with the formation of cytoplasmic protrusion ("buds"). Pole cell (or germ cell) specification starts from buds protrusions from the posterior embryonic cortex and followed by cellularization. Pole cell formation is under the control of the anterior-posterior gene patterning system. How the genetics and mechanics are intertwined to drive this morphogenetic process? We focus on mechanisms underlying the initial step of pole cell formation - budding. We employ a combination of live imaging techniques, genetic manipulations and mechanical perturbations to investigate the role of key players of budding. We take advantage of multi-view light sheet microscopy embryo imaging (low phototoxicity, 3D isotropic resolution) to characterize the dynamics of main cytoskeleton players during budding. Our preliminary data demonstrate that the myosin waves travel around posterior pole before and during pole cells budding.

24 - Rachedi Nesrine Safi – Axis 4

Dietary intake and glutamine-serine metabolism control pathologic vascular stiffness

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Keywords : Cardiovascular Disease, Metabolism, Vascular Fibroblast, Fibrosis, Collagen Metabolism

Perivascular collagen deposition by activated fibroblasts promotes vascular stiffening and drives cardiovascular diseases such as pulmonary hypertension (PH). Whether and how vascular fibroblasts rewire their metabolism to sustain collagen biosynthesis remain unknown. Here, we found that inflammation, hypoxia, and mechanical stress converge on activating the transcriptional coactivators YAP and TAZ (WWTR1) in pulmonary arterial adventitial fibroblasts (PAAF). Consequently, YAP and TAZ drive glutamine and serine catabolism to sustain proline and glycine anabolism and promote collagen biosynthesis. Pharmacologic or dietary intervention on proline and glycine anabolic demand decreases vascular stiffening and improves cardiovascular function in PH rodent models. By identifying the limiting metabolic pathways for vascular collagen biosynthesis, our findings provide guidance for incorporating metabolic and dietary interventions for treating cardiopulmonary vascular disease.

25 - Richter Margaux- Axis 5

Behavioural characterisation of a mouse model lacking the gene coding for augurin, a novel negative modulator of the canonical Wnt signalling pathway

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Keywords : Ecrg4/augurin – canonical Wnt signalling pathway – neurodevelopmental disordes –behavioural tests– hippocampal neurogenesis- sexual dimorphism

Esophageal cancer-related gene 4 (ECRG4) was first described as a gene downregulated in esophageal cancer and then identified by bioinformatics as encoding a peptide hormone termed augurin. We have shown a novel function for augurin as an inhibitor of the canonical Wnt signalling pathway. Signalling by the Wnt family of secreted glycolipoproteins is one crucial mechanism that regulates cell proliferation, cell polarity, and cell fate determination during embryonic development and tissue homeostasis. As a result, aberrant Wnt signalling underlies a wide range of human pathologies, including neurodevelopmental disorders. In this study we have investigated the consequences of the invalidation of Ecrg4 on some social and anxiety-related behaviours as well as on hippocampal neurogenesis. To this end we have used an Ecrg4 null mouse model . The battery of behavioural tests we have performed has revealed a social interaction deficit that appears at an adolescent stage and then disappears at an adult stage, increased anxiety-like behaviour, and cognitive deficits only in male Ecrg4 KO mice respect to control littermates. In contrast, female Ecrg4 KO mice displayed a social interaction deficit at an adult stage. Experiments of bromodeoxyuridine (BrdU) injections followed by immunohistochemical analyses revealed an altered neurogenesis in the hippocampus of male Ecrg4 KO mice, which correlates with the observed behavioural deficits. Those findings suggest that Ecrg4 KO mice might be a new experimental model of neurodevelopmental disorders, offering novel insights into the role of augurin, as a negative modulator of canonical Wnt signalling pathway, in brain development. Neurobiologists have long looked for differences between the brains of females and males that might explain sexually dimorphic behaviour. Intriguingly, the strong sexual dimorphism we show here is in line with the observation that several NeuroDevelopmental Disorders (as autism spectrum disorder, intellectual disability, schizophrenia) present a specific bias to males or to females. Our results suggest that sex-dependent regulation of brain development via the WNT pathway may lead to sex-dependent pathological alterations in brain maturation.

26 - Strazzulla Axelle– Axis 4

CD44 could aggravate liver fibrosis by regulating hepatic stellate cell functions

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Keywords : MASLD, Fibrosis, CD44, Hepatic stellate cell, TGFb

Background & aims: Liver fibrosis is the common response to chronic liver injury and leads to cirrhosis and its complications. Persistent inflammation is a driving force of liver fibrosis progression. In addition, liver collagen deposition associated with hepatic fibrosis is mainly dependent on proliferation, differentiation and activation of the hepatic stellate cells (HSCs). CD44, a glycoprotein mainly expressed in immune cells and HSCs, has been implicated in multiple inflammatory diseases but limited studies evaluated its role in liver fibrosis. We therefore explored its contribution to liver fibrosis in mice and patients and the regulation of HSCs functions. Methods: Hepatic CD44 was evaluated in mouse models of fibrosis and in obese patients with biopsy proven-metabolic dysfunction-associated steatotic liver disease (MASLD)(n=11). Its role in liver fibrosis was evaluated in global CD44 knock out mice and human hepatic stellate cell line (LX2). Results: Here, we report that hepatic CD44 expression correlated with liver injury and fibrosis in different mouse models of fibrosis. Interestingly, CD44 deficiency mediated a protective effect on fibrosis upon diet-induced fibrosis. Its hepatic gene expression was also upregulated with liver fibrosis and correlates with liver injury in biopsy-proven MASLD patients. In LX2 cell line, the silencing of Cd44 enhanced the cell mobility and the expression of inflammatory mediators including Il8, Il1b, Ccl2 and Cxcl1. This secretory environment was strongly amplified after LPS stimulation and diminished the pro-fibrogenic polarization of human blood monocyte-derived macrophages induced by IL4 stimulation. The Cd44 silencing also strongly modified the TGFb-mediated LX2 cell responses including a decreased expression of pro-fibrogenic mediators Acta2 and the key enzyme involved in the synthesis of Hyaluronic acid (HAS). Conclusion: Collectively, these data could suggest an important role of CD44 in the pathogenesis of liver fibrosis by regulating the migration, activation and secretory profile of hepatic stellate cells.

27 - Tanari Abdul Basith– Axis 1

Mechanics and mechanisms driving epithelial folding during gastrulation

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Keywords : Actomyosin cytoskeleton, Tissue mechanics, Embryoscale polarity, Gastrulation movements

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 end of 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 axis. 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 employing advanced light sheet imaging, quantitative live image analysis, optogenetics, and laser manipulation, our research will shed new light on the mechanics and mechanisms driving actomyosin polarity from the cell to the embryo scale, ultimately facilitating embryo gastrulation.

28 - Techer Hervé – Axis 3

MRE11 and TREX1 control senescence by coordinating replication stress and interferon signaling

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Keywords : Senescence, Oncogenic Stress, Replication Stress, TREX1, cGAS-STING

Oncogene-induced senescence (OIS) arrests cell proliferation in response to replication stress (RS) induced by oncogenes. OIS depends on the DNA damage response (DDR), but also on the cGAS-STING pathway, which detects cytosolic DNA and induces type I interferons (IFNs). Whether and how RS and IFN responses cooperate to promote OIS remains unknown. Here, we show that the induction of OIS by the H-RASV12 oncogene in immortalized human fibroblasts depends on the MRE11 nuclease. Indeed, treatment with the MRE11 inhibitor Mirin prevented RS, micronuclei formation and IFN response induced by RASV12. Overexpression of the cytosolic nuclease TREX1 also prevented OIS. Conversely, overexpression of a dominant negative mutant of TREX1 or treatment with IFN-β was sufficient to induce RS and DNA damage, independent of RASV12 induction. These data suggest that the IFN response acts as a positive feedback loop to amplify DDR in OIS through a process regulated by MRE11 and TREX1.

29 - Vayankara Edachola Sreeparvathy– Axis 3

Plasticity and composition of stress-induced RNA condensates

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Keywords : RNA condensates, heat shock, mRNA localization, oocyte fitness, RNA sequencing, fertility

The maintenance of cellular homeostasis requires precise spatiotemporal regulation of gene expression. A common post-transcriptional regulation is the formation of ribonucleoprotein (RNP) complexes comprising of mRNA bound to repressor proteins. These repressed mRNPs, at high cytosolic concentrations, can come together through liquid-liquid phase separation mechanisms to form large membrane-less RNA condensates capable of regulating mRNA storage, localization, translation and decay. This is especially important during environmental stress conditions, characterized by large-scale inhibition of translation and the formation of stress granules and large P-body like condensates. With most of literature studying stress-associated condensates with extreme temperatures or strong chemical stressors, we still lack a definite understanding of how RNA organizes itself on large-scale to protect against physiological stress. In our project, we study the formation, composition and plasticity of RNA condensates formed in the C.Elegans germline model during different temperature stress conditions. Previous studies from the lab (Cardona et al. Cell, 2023) had demonstrated how quiescence-induced P-bodies act to buffer the cytosolic mRNA concentration and protect the maternal mRNA pool to retain viability. We now hope to explore 1) the interaction, similarity and differences between the stress response and the quiescence response 2) the selectivity and composition of stress-induced RNA granules 3) understand the role of stress-induced RNA condensates in adapting to the stress. By visualizing RNA condensates at single-molecule resolution, we have showed an increase in local mRNA aggregation and embryonic lethality upon exposing worms to longer durations of physiological heat shock. However, we observe that quiescence before heat shock exposure reverses these phenotypes and increases embryo viability, suggesting a protective role for quiescence in adapting to the stress. In addition, we have purified stress-induced granules at 4°C and 32°C and sequenced their RNA transcriptome, enabling us to identify dramatic compositional change in granules. A careful analysis of the results and subsequent genetic approaches can let us understand the selectivity and adaptivity of RNA condensates. Overall, our research will provide a comprehensive understanding of the regulation of mRNA transcriptome in vivo during physiological stress.

30 - Vu To Giang – Axis 4

Lack of MDA5 delays HSC aging partly by retaining proteostasis

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Keywords: Hematopoietic stem cells, Aging, Stem cells, Inflammation

Alterations in the hematopoietic system characterized by inflammaging and immunosenescence are among the cornerstones of aging. How age-induced changes are controlled however remains largely unknown. Here, by investigating the role of the innate immune RNA sensor, melanoma differentiation-associated protein 5 (MDA5), we found its important role in hematopoietic stem cell (HSC) aging. Several hallmarks of aging were alleviated in the hematopoietic system of Mda5-/-. Overall, we observed decreased inflammation in aged Mda5-/- HSCs and their bone marrow (BM) microenvironment concurrent with reduced accumulation of aged and myeloid biased. These cellular changes were coupled with various alterations in metabolic parameters that pointed to a global delay in aging for Mda5-/ -HSCs. Concomitantly aged Mda5-/- HSCs remain more quiescent with better repopulation capacity than WT HSCs. Mechanistically, genome-wide and single cell analysis data indicated that HSF1, the master regulator of proteostasis, is the upstream regulator of the deregulated genes in aged Mda5-/- HSCs. Indeed, aged Mda5-/- HSCs retain better proteostasis while various beneficial aspects of the aging phenotypes could be reversed with the addition of HSF1 inhibitor. In contrast, different aging phenotypes in wild-type cells were rescued with HSF1 activator. Overall, our results show that attenuating Mda5 can delay the effects of aging in the HSC compartment by fine tuning inflammation and retaining active proteostasis.

31 - Wurtz Mickael – Axis 4

Regeneration as a tool to study the longevity in the sea anemone Nematostella vectensis

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Keywords : aging cnidarian stem cell regeneration

Aging is a complex, multifactorial process resulting in a progressive loss of physiological integrity, characterized by an increased susceptibility to death. Interestingly, not all living beings are equally susceptible to aging. Indeed, several marine organisms including some cnidarians (e.g., sea anemones, corals) appear to exhibit extreme longevity. Among them, the sea anemone N. vectensis does not show any apparent signs of aging over time. In order to determine the maximum lifespan of Nematostella vectensis and gain insight into the underlying cellular and molecular mechanisms we pursue various aims such as: 1) systematically characterizing longevity at the morphological, physiological, cellular and molecular levels over time; 2) attempting to perturb this longevity by applying chronic stress. Taking advantage of the strong regeneration capacities of N. vectensis, the chronic stress takes the form of successive amputation-regeneration cycles. This regeneration process is sustained by an increase in cell proliferation within the tissues of N. vectensis. Through these successive amputations, we aim to induce an accelerated exhaustion of the stem cells. Our preliminary results indicate stable reproduction and mortality rates and a constant telomere length in N. vectensis polyps up to eight years. Concerning the successive amputations, they appear to induce an increase in mortality. Interestingly, they're also inducing what might be age-associated morphological changes in the animals. Internal structures within N. vectensis, which appear to contain stem cell niches, are progressively disappearing after repeated amputations. And indeed, the success of regeneration events seem to be decreasing as well. Further investigations are still required to determine if those observations are correlated with a decline in the stem cell populations.

32 - Zhu Xiaoxuan– Axis 3

Role of FERONIA during Plant-Oomycete interactions: trojan horse or true defender?

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Keywords : Arabidopsis, Marchantia, Oomycete, Cell wall integrity, CrRLK1L

Plant cells have evolved complex signaling pathways to coordinate intracellular growth with the extracellular cell wall, which protects them from the external environment. These pathways, known as cell wall integrity (CWI) mechanisms, are regulated by receptor-like kinases in higher plants, including FERONIA (FER). Subsequently, FER was identified to function as an essential regulator in pleotropic biological processes, receiving a considerable interest in the plant immune responses. In this study, we report that FER is positively involved in Arabidopsis immunity against Phytophthora palmivora, an oomycete species with a broad host range. The Atfer-4 mutant shows increased susceptibility to P. palmivora infection as early as 10 hours post-infection (hpi), whereas the complementary line Atfer-4+FER-GFP displays WT-like resistance. Additionally, the signaling partners of FER, LORELEI-like-GPI-AP1 (LLG1) and leucine-rich repeat extensin proteins (LRXs), also contribute positively to the immune response against P. palmivora. Interestingly, while FER-mediated CWI mechanisms in tip-growing cells are conserved in the early-diverging land plant Marchantia polymorpha, FER-mediated immune responses to P. palmivora seem more complex. Indeed, Mpfer shows significantly less symptoms than wild-type plants after P. palmivora infection, along with delayed P. palmivora growth and reduced expression of defense-related genes in Marchantia. These results suggest that FER negatively regulates Marchantia defenses against P. palmivora. Taken together, our research reveals that FER plays distinct roles during plant-oomycete interactions. In the early-diverging land plant Marchantia, FER signaling appears to be manipulated by P. palmivora to establish disease while the flowering plant Arabidopsis, utilizes FER signaling to defend itself against P. palmivora infection.

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