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April 03, 2024 - Lyon

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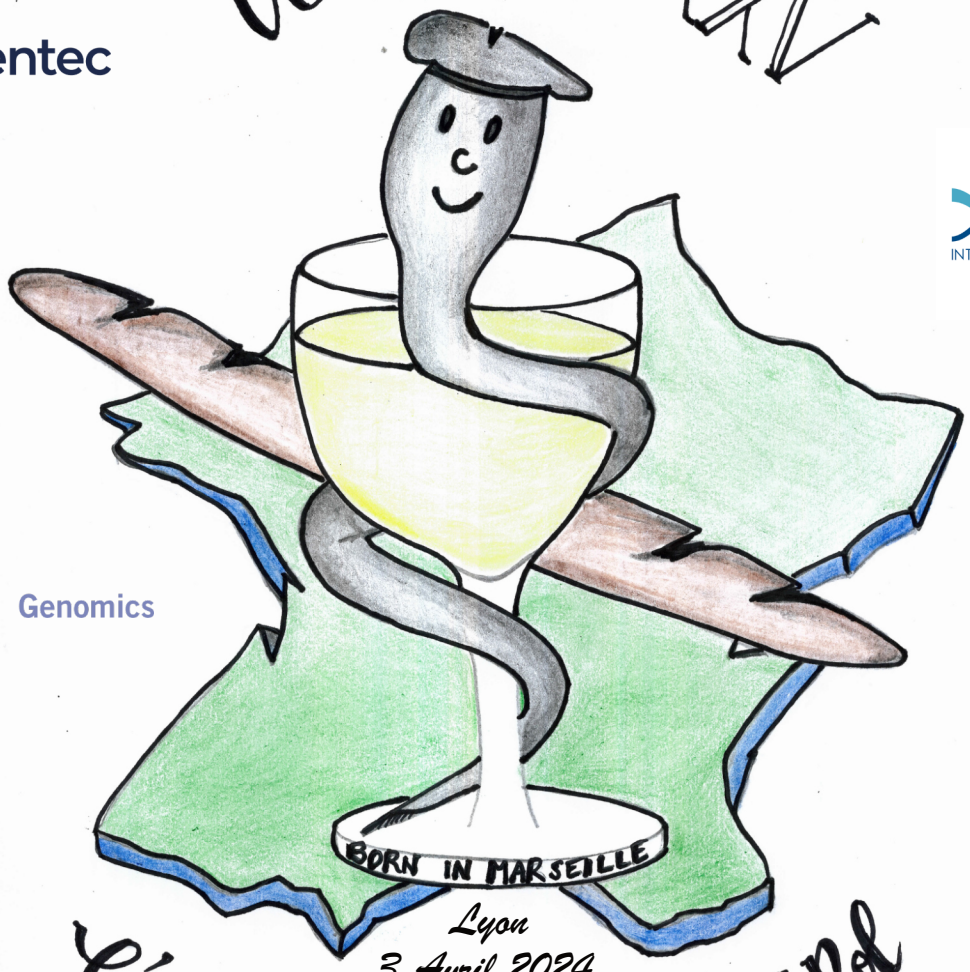

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Ver Midi XXV

Wednesday April 03 2024

Amphi Charles Mérieux (Place de l'École, ENS de LYON)

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9h55-10h00 Opening by the organisers

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Elise Cheynet (MeLiS, Lyon)

10h20-10h40 *C. elegans* as a model system for the study of human non-muscle actinopathies
Théo Hecquet (IGBMC, Strasbourg)

10h40-11h00 Mechanical coupling of aECM to the epidermis
Jeanne Eichelbrenner (CIML, Marseille)

11h00-11h15 A word from our sponsors

11h15-11h30 **Short break**

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Neuromodulation by wireless neuropeptidergic signaling networks

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14h00-14h20 TMED-3 is a selective regulator of heteromeric acetylcholine receptors biosynthesis
Greta Maiellano (MeLiS, Lyon)

14h20-14h40 Synergistic processing of sensory modalities underlies the evolution of predatory behaviours in the nematode *Pristionchus pacificus*
Marianne Roca (MPINB, Germany)

14h40-15h00 A role for transposons in the evolution of programmed DNA elimination in *Mesorhabditis* nematodes
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15h00-15h20 Deciphering the multiple pathways to avoid sperm mitochondria inheritance
Valentine Melin (IBPS, Paris)

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Ludivine Roumbo (IJM, Paris)

16h40-17h00 Uncovering molecular mechanisms for developmental synchrony with in-vivo spatial temperature perturbations in *C. elegans* larva
Eliot Schlang (Institut Curie, Paris)

17h00-17h20 Wnt ligands mobility in *C. elegans* embryos
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17h20-17h30 Oral presentation and poster prize, concluding remarks

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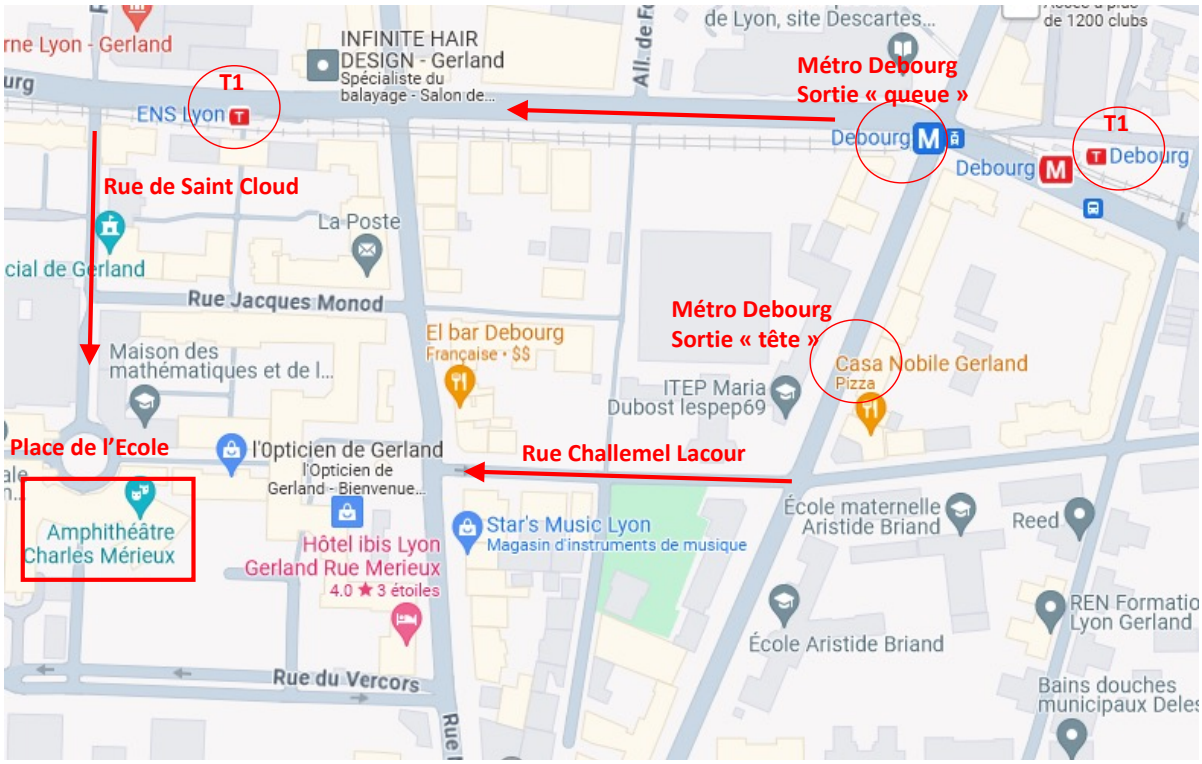
CAMPUS MAP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GUEST SPEAKER

Isabel Beets

(KU Leuven)

"Neuromodulation by wireless neuropeptidergic signaling networks"

Zels, S., Watteyne, J., Ripoll-Sanchez, L., Vandewyer, E., Schafer, W.R., Vértes, P.E., Mirabeau, O., Schoofs, L., Beets, I.

Neuropeptides are widespread in all nervous systems and constitute an extrasynaptic signaling network by binding to a variety of G protein-coupled receptors (GPCRs). These wireless neuromodulatory interactions are critical to the function of all animal brains and regulate almost all behaviors and physiological processes. To probe the structure and function of the peptidergic signaling network, we have mapped the peptide-GPCR network in the nematode *C. elegans*. Due to its compact and well-defined nervous system, *C. elegans* provides an attractive model to functionally characterize the neuropeptidergic network. Using reverse pharmacology, we have identified 461 cognate peptide-GPCR couples in *C. elegans*, many of which are evolutionarily conserved between the wormand other animals. These peptide-GPCR pairs are organized in a broad signaling network that exhibits a high density of connections, with specific and combinatorial interactions encoded across and within single peptidergic genes. The topology of the neuropeptide network also differs from that of other signaling networks, such as synaptic connectomes. We are using this map along with *in vivo* sensors for GPCR activity to better understand the functional organization and the plasticity of neuropeptidergic networks. This neuropeptide connectome lays a foundation for system-level analysis of neuropeptidergic modulation.

SPONSORS & ACKNOWLEDGEMENTS

We would like to thank Sophie Quintin for her art work on the Ver Midi XXV cover.

We are very grateful to our numerous sponsors.
This year's free meeting would not have been possible without the generosity of our sponsors, whom we encourage you to visit during the day.

The organizing committee,
Bérangère Pinan-Lucarré, MeLiS
Mélissa Cizeron, MeLiS
Florence Solari, MeLiS
Manuela D'Alessandro, MeLiS
Valérie Robert, LBMC

ENS de Lyon
L'ENS de Lyon forme par et pour la recherche des étudiants motivés, qui ont le désir d'apprendre. Elle regroupe toutes les disciplines en dehors du droit et de la médecine. À l'École, la formation obéit à 3 règles : la promotion d'approches multidisciplinaires, le suivi individualisé des parcours adaptés aux projets des étudiants, la nécessité de respecter le

temps long de la recherche. Cette formation est étroitement associée à une recherche fondamentale, reconnue en France comme à l'international.

Université Claude Bernard Lyon 1
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La Société Française de Biologie du Développement est une société savante qui fédère depuis plus de 50 ans les chercheurs travaillant dans le domaine de la Biologie du Développement animale ou végétale.

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Leica Microsystems développe et fabrique depuis 175 ans des microscopes et instruments scientifiques pour l'analyse de microstructures et nanostructures. Largement reconnue pour ses outils de précision optique et sa technologie innovante, la société figure parmi les leaders du marché en matière de stéréomicroscopie et de microscopie photonique, de microscopie numérique, de microscopie confocale à balayage laser et de microscopie de super-résolution avec systèmes d'imagerie associés, de préparation d'échantillons en microscopie électronique.

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MeLiS teams are interested in the molecular mechanisms operating in a variety of cellular compartments, from cilia, membranes, axons, to synapses and circuits, with a focus on neuronal and muscular cells. We investigate a range of biological processes and their alterations in human diseases affecting developing, adult and aging organisms.

SESSION 1

Wnt-Ror-Dvl signalling controls cellular and tissue polarity in *C. elegans* muscles, **Elise Cheynet** (MeLiS, Lyon)

Wnt-Ror-Dvl signalling controls cellular and tissue polarity in C. elegans muscles

Elise Cheynet*[1], Sandra Duperrier[1], Alice Peysson[1], Amandine Chambert-Loir[1], and Thomas Boulin[1]

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Abstract

Cell polarity mechanisms allow the formation of specialized membrane domains with unique protein compositions, signalling properties, and functional characteristics.
By studying the localization of potassium channels in *C. elegans* body wall muscles, we have discovered an entirely unsuspected case of membrane compartmentalization and planar cell polarity. Indeed, we have found that TWK-28 channels are enriched at the anterior tip of muscle cells, while SLO-1 channels are only found in the posterior half of each cell. In addition, proteins of the Dystrophin complex that are required for the surface expression of TWK-28 and SLO-1, also display asymmetric subcellular localizations.

A candidate gene approach revealed that this cellular and tissue polarity is controlled by a non-canonical Wnt signalling cascade involving the ligand EGL-20/Wnt, the receptor CAM-1/Ror, and the intracellular effector DSH-1/Dishevelled. Interestingly, it does not require classical planar cell polarity proteins.

We seek to further understand the cellular and molecular mechanisms controlling the polarized organization of the worm's sarcolemma.

In order to better understand how the Wnt-Ror-Dvl pathway works and to find additional regulators, we performed an unbiased visual screen, looking for mutants that disrupt polarity. We identified three new conserved proteins involved in muscle polarity. Remarkably, two of these proteins themselves display a polarized distribution.

Combining CRISPR genome edition and knock-in reporter lines, we are investigating their relationship to the Wnt-Ror-Dvl signalling pathway.
This novel example of planar cell polarity in a tractable genetic model organism thus allows us to dig into the mechanisms of a conserved signalling pathway, and its use to regulate cellular organization, allowing specific functions to be compartmentalized within a single cell.

Keywords: polarity, muscles

*Speaker

C. elegans as a model system for the study of human non-muscle actinopathies**, Théo Hecquet** (IGBMC, Strasbourg)

C. elegans as a model system for the study of human non-muscle actinopathies

Théo Hecquet*[1], Nadine Arbogast[1], Delphine Suhner[1], Anaïs Goetz[1], Grégory Amann[1], Johannes N. Greve[2], Nataliya Di Donato[2], and Anne-Cécile Reymann[1]

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[2]Medizinische Hochschule Hannover = Hannover Medical School – Germany

Abstract

Actin is a protein that self-assembles into a dynamic network essential for physiological processes such as cell migration or division. Single point missense mutations, frameshift mutations, truncating mutations or gene deletions in the human cytoplasmic actin coding genes ACTB and ACTG1 lead to ultra-rare disorders, termed Non-Muscle Actinopathies (NMA). Patients presenting NMA develop a wide range of symptoms with different severities, notably in terms of intellectual disability and facial or organ malformations. To date, a definitive genotype-to-phenotype correlation within the NMA field has yet to emerge, and the functional mechanisms underlying symptoms in patients remain elusive. To fill this gap, we propose to realise a multi-scale phenotypic characterization of *Caenorhabditis elegans* strains with actin variants*:* from general animal fitness to stereotypical organization and development, as well as cell-scale events or molecular dynamics.
The focus of this project is thus to investigate whether classification of NMA matches in the model *C. elegans* as well as decipher if we can predict the severity of symptoms linked to *de novo* single point mutations associated with NMA.

Ten human substitutions, chosen to span a large range of severity in patients, were successfully recapitulated in *C. elegans* actin-coding gene *act-2* using CRISPR/Cas9 mediated genome engineering. Interestingly, our preliminary results highlight that the general healthiness of mutant worms is correlated with patients' disease severity. Indeed, three variants corresponding to some of the most severe forms of NMAs caused homozygously non-maintainable strains. Using a variety of techniques, we then assess the consequences of individual actin variants at different scales; from general worm fitness to embryo development up to *in vivo* molecular dynamics. Overall, we observed the presence of variant-specific defects with different penetrance linked to actin biomechanics, such as gonad malformations or cell blebs. We also observe variant-specific embryo arrest during key events of development, namely the first cell division, gastrulation, ventral enclosure and before the second step of elongation. Nonetheless, we did not detect major changes in motility, touch response, or neuron positioning and identity in surviving worms.

*Speaker

Mechanical coupling of aECM to the epidermis

Jeanne Eichelbrenner*[1], Natalie Pujol[1], Michel Labouesse[2], and Thomas Sonntag[1]

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[2]Laboratoire de Biologie du Développement [IBPS] – Sorbonne Universite, Centre National de la Recherche Scientifique, Institut de Biologie Paris Seine – France

Abstract

All multicellular organisms must protect themselves from injury and pathogens. Lacking an adaptive immune system or motile immune cells, C. elegans relies on its epithelial barrier to defend against environmental threats. This makes it a powerful model to address the question of how epithelial cells detect damage. In C. elegans, the skin is characterized by a rigid but flexible apical extracellular matrix (aECM), the cuticle, which surrounds and protects the epidermis. Like the cell wall of plants or yeast, the nematode aECM also provides mechanical support to the underlying epithelium. Several features led us to postulate that the epidermis mechanically monitors the integrity of the aECM. We found that any change in cuticle mechanics, such as during molt when the aECM is remodeled, or in mutants of certain collagens with a change in matrix stiffness , induces a prophylactic immune response in the epidermis, similar to that induced during infection or damage. During molting, mechanical support is thought to be transiently transferred to the cytoskeleton, thanks to actin and microtubules alignment in periodic circumferential bands along the whole worm in the epidermal cell (Aggad et al., 2023). How does the epidermis read the changes in the aECM mechanics and induce coordinated cytoskeletal rearrangements and an immune response? To answer this question, we are currently exploring the mechanosensitivity of the different structures at the interface of the aECM and the epithelium. Using molting as a proxy for mechanical changes, we have observed specific transitory alignment of several structures, each appearing and disappearing at a precise timing during the formation of the new cuticle. We found attachment structures like hemidesmosomes and meisosomes, but also cytoskeleton regulators like spectrins and non muscle myosins that are concomitant to actin and microtubule alignment. While doing a precise time series of appearance of these aligned structures, we are running epistasis analysis to explore their intimate dependency. In parallel, we have run genetic screens that led so far to the isolation of several candidates altering the immune response, including caderin and microtubule regulators and are exploring their role in the mechanical response of the epidermis during molting. We expect to discover potentially novel signaling pathways involved in the mechanical coupling of the aECM to the epidermis.

Keywords: Extracellular matrix, Mechanotransduction, Cytoskeleton

*Speaker

SESSION 2

TMED-3 is a selective regulator of heteromeric acetylcholine receptors biosynthesis

Greta Maiellano*[1], Manuela D'alessandro[1], and Jean-Louis Bessereau[1]

[1]MeLis, CNRSUMR5284, INSERMU1314, InstitutNeuroMyoGene, Universite de Lyon, Universite Claude Bernard Lyon 1, Lyon, France – University of Lyon, University Claude Bernard Lyon 1, MeLiS, CNRS UMR5284, INSERM U1314 – France

Abstract

Acetylcholine receptors (AChRs) are neurotransmitter receptors found both in the nervous system, where they modulate synaptic transmission, and at the neuromuscular junction (NMJ), where they permit muscle contraction. AChRs belong to the family of the Cys-loop receptors, which are composed of 5 subunits. AChRs can be either homo- or hetero-pentamers and their composition is regulated at many levels. Since impairments in AChRs expression and composition are associated with several neurological and muscular pathologies, we aim to characterize new regulators of their biosynthesis and composition using *C. elegans*. At the NMJ of *C. elegans* the muscle is innervated by both cholinergic and GABAergic terminals and therefore presents three main types of Cys-loop receptors at the plasma membrane, namely the GABAergic receptors (GABAAR), the homomeric nicotine-sensitive AChRs (N-AchRs) and the heteromeric levamisole-sensitive AChRs (L-AChRs). In a forward genetic screen performed in *C. elegans*, we identified *tmed-3* and *sel-9* as two genes required for the expression of heteromeric L-AChRs at the NMJ. TMED-3 and SEL-9 are homologues of human TMED7 and TMED2 respectively, two members of the transmembrane emp-24 domain (TMED) proteins. TMED proteins are endoplasmic reticulum- and Golgi-resident transmembrane proteins responsible for the anterograde and retrograde transport of cargos by the COPI (COatomer Protein complex I)- and COPII-coated vesicles. The TMED protein family is divided into four subfamilies (alpha, beta, gamma and delta). In *C. elegans* only one member of each subfamily is expressed in body wall muscle cells, except for the gamma-subfamily with two members, TMED-3 and TMED-1. We have shown that TMED proteins act as a tetrameric complex that requires the presence of at least one of each subfamily member to be functional and stable. This tetramer is required for the expression of Cys-loop receptors located on the postsynaptic membrane of the muscle (L-AChR, N-AChRs and GABAARs), since knock-out of each subfamily results in an equivalent loss of receptors at the NMJ. Interestingly, TMED-3 is selective for L-AChRs and TMED-1 can not replace its function. We hypothesize that the TMED-3-containing tetramers are required for the trafficking of L-AChRs possibly acting as a cargo sorting adaptor.

Keywords: acethylcholine receptors, transmembrane emp, 24 domain proteins, protein biosynthesis

*Speaker

Synergistic processing of sensory modalities underlies the evolution of predatory behaviours in the nematode Pristionchus pacificus

Marianne Roca*[1], Güniz Göze Eren[2], Leonard Böger[1], Wen-Sui Lo[3], and James Lightfoot[1]

[1]Max Planck Institute for Neurobiology of Behavior - caesar – Germany
[2]Max Planck Institute for Neurobiology of Behavior - caesar – Germany
[3]Norhwest AF University – China

Abstract

Sensory systems are the primary interface between an organism and its environment and changes in their selectivity or sensitivity are a key toward behavioural evolution and diversity. In nematodes, different species utilise diverse nutrient resources and have acquired sensory adaptations and behaviours specific for their ecological niche. Here, we exploit these differences to investigate sensory system plasticity and its importance for behavioural evolution. In comparison to the microbial feeder *Caenorhabditis elegans,* the omnivorous species *Pristionchus pacificus* has evolved predatory behaviours which are dependent upon direct nose contact with prey. Therefore, to explore the evolution of mechanosensory adaptations and its role in prey detection, we identified 22 potential mechanosensory genes and generated CRISPR/Cas9 mutants for each of these. We identified a conserved function in touch response between *C. elegans* and *P. pacificus* for *Ppa-mec-3, Ppa-mec-4, Ppa-mec-10* and *Ppa-mec-6.* However, in *P. pacificus*, we find *Ppa-mec-3* and *Ppa-mec-6* are additionally involved in their prey detection ability. Importantly, mutations in the master regulator of cilliogenesis *Ppa-daf-19* also show reduced prey detection due to chemosensory rather than mechanosensory defects. Subsequently, mutations affecting both sensory modalities resulted in a more severe prey detection defect demonstrating the co-option of both sensory inputs have contributed to the evolution of predatory behaviours. Finally, using newly developed automated behavioural tracking methods alongside machine learning models we are currently exploring how these sensory defects affect behavioural states. Thus, predatory behaviours in *P. pacificus* are dependent on the synergistic processing of chemosensory and mechanosensory modalities reinforcing the importance of sensory systems for the evolution of behavioural novelties.

Keywords: behaviour, mechanosensation, chemosensation, predation, pristionchus

*Speaker

A role for transposons in the evolution of programmed DNA elimination in Mesorhabditis nematodes

Brice Letcher*[1], Lewis Stevens[2], Caroline Launay[1], Eva Wenger[1], Mark Blaxter[2], and Marie Delattre[1]

[1]Laboratory of Biology and Modelling of the Cell – CNRS : UMR5239, École Normale Supérieure - Lyon – France

[2]The Wellcome Trust Sanger Institute [Cambridge] – United Kingdom

Abstract

While we commonly assume that individual organisms carry an identical genome across cells and tissues, a number of eukaryotic species undergo Programmed DNA Elimination (PDE), the destruction of parts of chromosomes in somatic cells during normal development. How and why PDE occurs has remained largely unresolved, largely due to a lack of lab-tractable models and insufficiently complete sequencing data (e.g., high-fidelity long-reads). We recently discovered that species of Mesorhabditis, a genus of lab-tractable nematode worms, undergo substantial PDE during early development (_˜30% of the genome is lost). In this talk, I will introduce the PDE process in Mesorhabditis and how we are resolving it using a mixture of experimental and computational approaches. I will then focus on how, using a combination of PacBio Hi-Fi, Illumina and Hi-C data, we could resolve elimination breakpoints, and how our results suggest transposons play an active role in the short- and long-term evolution of PDE, and could act as effectors of the PDE process itself.

Keywords: Programmed DNA Elimination, Genome Evolution, Transposable elements, Genome cutting, Soma/Germline Differentiation, Development

*Speaker

Deciphering the multiple pathways to avoid sperm mitochondria inheritance

Valentine Melin*[1], Justine Cailloce , Fanny Husson , Jorge Merlet , and Vincent Galy

[1]C. elegans Heredity and development – Sorbonne Université - CNRS UMR7622 - Institut de Biologie Paris-Seine – France

Abstract

Mitochondria are essential intracellular organelles in eukaryotes cells allowing multiple biological pathways, including energy production. They contain their own genome (mtDNA) which represents only a small fraction of the cell's genes, but which are nevertheless vital. In many eukaryotes' species, while nuclear genome is equally inherited from both parents, mitochondria and mtDNA are exclusively maternally inherited. Despite significant progresses in understanding how this is achieved, the consequences of abnormal biparental heredity remains unknown mostly because this is still not experimentally possible to prevent sperm-derived mtDNA clearance.
In *C. elegans*, sperm mitochondria enter the embryo and are quickly and actively degraded by a specific autophagy pathway involving the allophagic receptor ALLO-1. Moreover, the endonuclease CPS-6 is involved in degradation of sperm-derived mtDNA while FNDC-1 and PHB-2, two mitophagy receptors, participate in sperm mitochondria clearance. Importantly, in each single mutants, sperm mitochondria were described as transiently stabilized but not established and inherited in the adult offspring. In order to clarify the functional interactions and respective contributions of these factors and try to prevent the clearance of sperm mitochondria, I constructed mutant lines with the simultaneous inactivation of these factors. I will present our functional characterization of the different combination of mutations and how we revealed that additional important factors and pathways exist to ensure the degradation of sperm mitochondria and to prevent the transmission of sperm-derived mitochondria to the offspring.

Keywords: mitochondria, inheritance, mtDNA

*Speaker

SESSION 3

The single MAST kinase KIN-4 phosphorylates ENSA-1 to inhibit the PP2A-B55 phosphatase and regulate mitotic entry in C. elegans

Ludivine Roumbo*[1], Batool Ossareh-Nazari[1], Suzanne Vigneron[2], Lucie Van Hove[1], Benjamin Lacroix[2], Anna Castro[2], Nicolas Joly[1], Thierry Lorca[2], and Lionel Pintard[1]

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[2]Centre de recherche en Biologie cellulaire de Montpellier – Centre National de la Recherche Scientifique, Université de Montpellier – France

Abstract

Regulation of the timing of mitotic entry contributes to the acquisition of cell-type specific cell cycle duration during animal development. With its asynchronous and stereotyped divisions, the *C. elegans* embryo represents a model of choice for dissecting how mitotic kinases, notably Cyclin B-Cdk1 and its opposing phosphatase PP2A-B55, control the precise timing of mitotic entry. However, the molecular mechanisms regulating B55 activity are elusive in *C. elegans*. Notably, the Greatwall/MAST-L (Microtubule-Associated Serine/Threonine kinase-like) kinase, which inhibits B55 in other systems, is absent in *C. elegans*. Here, we identify and functionally characterize a new pathway inhibiting B55 activity in *C. elegans* embryos. In this pathway, the single worm MAST kinase KIN-4 (KINase 4), previously associated with aging and thermotaxis phenotypes, directly phosphorylates ENSA-1, the single worm endosulfine, and converts it into a B55SUR-6 inhibitor. Inactivation of this pathway robustly suppresses the embryonic lethality, the cell cycle timing, and vulval development defects observed in embryos and animals with reduced B55 phosphatase activity. We show that *C. elegans* KIN-4 can functionally replace the Greatwall kinase in the heterologous Xenopus system. Our findings resolve a long-standing paradox on the presumed absence of a Greatwall-like pathway in *C. elegans* and highlight a new aspect of B55 regulation.

Keywords: Greatwall pathway, Cell cycle, Development, PP2A, B55, MAST kinase

*Speaker

Uncovering molecular mechanisms for developmental synchrony with in-vivo spatial temperature perturbations in C. elegans larva.

Eliot Schlang*[1], Marie-Caroline Jullien[2], Simon Berger[3], Grégoire Clément[4], and Wolfgang Keil[1]

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[2]Institut de Physique de Rennes – Université de Rennes, Centre National de la Recherche Scientifique – France

[3]Department of Molecular Life Science, University Zürich, Winterthurerstrasse 190, 8057 Zürich, Switzerland. Institute for Chemical- and Bioengineering, ETH Zürich, Vladimir Prelog Weg 1, 8093 Zürich, Switzerland – Switzerland

[4]Gulliver UMR CNRS 7083, ESPCI Paris, Université PSL, 10 rue Vauquelin, 75005 Paris, France – Gulliver CNRS UMR 7083 – France

Abstract

The development of multicellular organisms is strikingly robust with respect to environmental fluctuations such as nutrient availability, oxygen level, or presence of pheromones. One example of this robustness is the fact that poikilothermic animals greatly change their rates of development as a function of ambient temperature without any loss in developmental precision and invariant developmental outcomes over wide temperature ranges. How this robustness is achieved is not well understood.
Here, we focus specifically on the adaption of developmental rate of cold-blooded animals to changes in temperature and ask to what extent cell-cell communication contributes to robust temperature scaling of development. Our approach is to subject developing C. elegans larvae to steep linear temperature gradients of about 10C/mm along their anteroposterior axis.

To this end, based on the microfluidic designs developed by Berger et. al. (2021) and the temperature control system relying on an optimized set of resistors micropatterned onto a coverslip developed by Selva, Jullien et al. (2009), we engineered a novel microfluidic system that combines confinement of feeding and growing elongated larva with precise spatiotemporal temperature control at the scale of 10-50um. This enables long-term high-resolution ¬in-vivo imaging of larvae developing in steep temperature gradients. Using this system, we uncovered that hypodermal stem cell division timings which normally occur synchronously through the anteroposterior axis in each larval stage, remain synchronized, even after prolonged exposure to strong temperature gradients. This striking result suggests that cell-cell communication underlies robust temperature scaling. We are also investigating whether synchrony of somatic gonadal migration is maintained under these conditions focusing on Distal Tip Cells turn.

*Speaker

Wnt ligands mobility in C. elegans embryos

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Abstract

Multiple processes in animal development are regulated by signaling molecules that control tissue patterning and cell fates. However, the specific spatial and temporal dynamics of the spreading of these molecules often remain unknown, even though they determine the length scales and time frames of signal activity. The establishment of concentration gradients through morphogen diffusion is a commonly proposed mechanism, despite limited in vivo measurements of these gradients. More generally, the modes of morphogen dispersion in tissue are still unclear, with only a few exceptions. To address these gaps, we investigated the mobility of Wnt ligands, a conserved family of signaling proteins, in *C. elegans* embryos. We demonstrated that Wnts are expressed in the posterior half of the embryo with single-molecule Fluorescence In Situ Hybridization (smFISH). Additionally, through quantitative live imaging of endogenously tagged ligands, we observed their secretion and intercellular dispersion. Importantly, we measured that these ligands can diffuse throughout the tissue in a timescale shorter than the cell cycle. To quantify their diffusion, we determined the diffusion coefficient of Wnt ligands using Fluorescence Correlation Spectroscopy (FCS). Combining our experimental measurements with numerical simulations, we established that the diffusion of Wnt ligands is sufficiently rapid to polarize target cells in the anterior half of the embryo, even at a distance from the Wnt source. Consequently, our findings provide support for a diffusion-based, long-range Wnt signaling mechanism consistent with the dynamics of developmental processes.

Keywords: Wnt, diffusion, biophysics, polarity

*Speaker

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POSTERS

Characterization of a new muscle-aging regulator

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Abstract

The aging process is associated with a progressive decline in mobility in many species, including *C.elegans*. This loss of mobility results from both neuronal and muscular degeneration (Liu *et al.*, 2013; Mergoud dit Lamarche *et al.*, 2018). Our team has characterized the subcellular changes that take place during muscle aging and that are also observed in skeletal and cardiac muscle during human aging (gene expression, mitochondrial fragmentation and autophagy blockade). We previously identified the receptor DAF-2/Insulin-IGF-1 and the transcription factor UNC-120/SRF as modulators of these biomarkers and mobility with age (Mergoud dit Lamarche *et al.*, 2018). Both act cell-autonomously to regulate muscle ageing, independently of their impact on lifespan (Mergoud dit Lamarche *et al.*, 2018; Roy *et al.,* 2022).
In order to identify new regulators of muscle ageing, we have set up a screen based on the monitoring of muscle biomarkers in live animals after random mutagenesis. We will present preliminary data on the characterization of a mutant isolated from this screen, which revealed an unexpected function for a protein well known for its role in muscle contraction.

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Keywords: Muscle, Aging

*Speaker

Constitutive sodium permeability in a C. elegans two-pore domain potassium channel

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Abstract

Two-pore domain potassium (K2P) channels play a central role in modulating cellular excitability and neuronal function. The unique structure of the selectivity filter in K2P and other potassium channels determines their ability to allow the selective passage of potassium ions across cell membranes. The nematode *C. elegans* has one of the largest K2P families, with 47 subunit-coding genes. This remarkable expansion has been accompanied by the evolution of atypical selectivity filter sequences that diverge from the canonical TxGYG motif. Whether and how this sequence variation may impact the function of K2P channels has not been investigated so far. Here we show that the UNC-58 K2P channel is constitutively permeable to sodium ions and that a cysteine residue in its selectivity filter is responsible for this atypical behavior. Indeed, by performing *in vivo* electrophysiological recordings and Ca2+ imaging experiments, we demonstrate that UNC-58 has a depolarizing effect in muscles and sensory neurons. Consistently, *unc-58* gain-of-function mutants are hypercontracted, unlike the relaxed phenotype observed in hyperactive mutants of many neuromuscular K2P channels. Finally, by combining molecular dynamics simulations with functional studies in *Xenopus laevis* oocytes, we show that the atypical cysteine residue plays a key role in the unconventional sodium permeability of UNC-58. As predicting the consequences of selectivity filter sequence variations *in silico* remains a major challenge, our study illustrates how functional experiments are essential to determine the contribution of such unusual potassium channels to the electrical profile of excitable cells.

Keywords: K2P potassium channels, UNC, 58, ion channel selectivity

*Speaker

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SIN-3 transcriptional coregulator maintains mitochondrial homeostasis and polyamine flux

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Abstract

Mitochondrial function relies on the coordinated transcription of mitochondrial and nuclear genomes to assemble respiratory chain complexes. Across species, the SIN3 coregulator influences mitochondrial functions, but how its loss impacts mitochondrial homeostasis and metabolism in the context of a whole organism is unknown. Exploring this link is important because *SIN3* haploinsufficiency causes intellectual disability/autism syndromes and SIN3 plays an important role in tumor biology. Here we show that loss of *C. elegans* SIN-3 results in transcriptional deregulation of mitochondrial- and nuclear-encoded mitochondrial genes, potentially leading to mito-nuclear imbalance. Consistent with impaired mitochondrial function, *sin-3* mutants show extensive mitochondrial fragmentation by transmission electron microscopy (TEM) and *in vivo* imaging, and altered oxygen consumption. Metabolomic analysis of *sin-3* mutant animals identifies a signature of mitochondria stress and deregulation of methionine flux, resulting in decreased S-adenosyl methionine (SAM) and increased polyamine levels. Our results identify SIN3 as a key regulator of mitochondrial dynamics and metabolic flux, with important implications for human pathologies.

Keywords: SIN3/HDAC, mitochondrial dynamics, metabolic flux

*Speaker

Estimation of mRNAs stability genome-wide through combined analysis of GRO-seq and RNA-seq data in C. elegans.

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Abstract

We have recently discovered that the LSM2-8 complex mediates a mechanism of RNA degradation that selectively targets H3K27me3-marked genes in *C. elegans*.It reveals that, in animals, heterochromatin can be silenced by specific degradation of heterochromatic transcripts, and not only by transcriptional repression. Therefore, we are interested in post-transcriptional mechanism(s) involved in heterochromatin silencing in higher eukaryotes.
RNA decay assays allowing to measure RNA stability were assessed only on subsets of LSM-8 regulated genes. Here, we further investigate the link between the RNA stability and the selective targeting of the LSM2-8 complex to H3K27me3-marked genes in a genome wide manner using a novel approach.
Current experimental approaches for measuring RNA stability are generally labor-intensive, limited in sensitivity, and/or disruptive to normal cellular processes. Thus, prior to in vivo experiments, we performed in silico tests. For that, we use a recent and simple bioinformatic method for estimating relative RNA half-lives, demonstrated in *Blumberg, et al.* in 2021 that we apply to *C. elegans*. *Blumberg et al.* showed that this approach has good accuracy and sensitivity for both coding and noncoding transcription units. This method is based on two high-throughput assays: Global Run-On sequencing (GRO-seq) or other methods to measure nascent RNA, and RNA sequencing (RNA-seq) as a measure of RNA steady-state concentration. Based on these method, different classes of RNA stability can be defined (for example high, medium and low stable RNA). Interestingly, in mammalian cells, *Blumberg et al.* showed that H3k27me3 coding genes are enrished in the low stable RNA classe.
In this work, we used GRO-seq and RNA-seq published datasets from the same biological replicates, in early L4 wild type in *C. elegans* (N2, Cornes et al., 2022). Especially, we were interrested in testing whether LSM-8 regulated genes or H3K27me3 marked genes correlate with a particular class of RNA stability.

Keywords: Bioinformatics, mRNA stability estimation, RNA, seq, GRO, seq, ChIP, seq analysis, Multiomics, LSM8

*Speaker

Muscular contractions shape the intestine of C. elegans.

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Abstract

During embryogenesis, C. elegans embryo elongates 4 times. This substantial morphogenetic event is driven by body wall muscle contractions starting from the two fold stage. Concomitantly, intestinal cell reshape their apical domain to grow brush border. We therefore asked if mechanical constraints due to muscle contractions were instrumental in gut morphogenesis.

To tackle this question we compared brush border formation using the endogenously tagged brush border marker ERM-1 in control and paralyzed embryos. Embryos were paralyzed via interfering RNA targeting genes specifically expressed in the body wall muscles. This approach is leading to a well characterized embryonic elongation arrest known as the paralyzed at twofold phenotype (*pat* phenotype).

ERM-1 was apically localized in control and pat RNAi embryos. Thus muscular contractions are dispensable for intestinal cell polarity and construction of the brush border.
However, the length of the intestinal lumen of *pat* RNAi embryos was overly elongated, with measures comparable to the one observed in 3 to 4 fold embryos.

To understand if the over elongated lumen reflected a global growth defect of the intestine or was due to an excessive expansion restricted to the apical domain of intestinal cells, we first reproduced the *pat* phenotype in the end-1p::GFPcaax strain where all intestinal cell membranes are labelled by GFP. In *pat* RNAi embryos the length of intestine was similar to control whereas the length of the intestinal lumen was aberrantly greater than the length of the intestine.

Hence, muscular contractions are required for proper elongation of the intestine. Moreover, our analysis based on two D pictures show that the extension of the apical domain on the worm longitudinal axis does not correlate with the basal domain extension in pat embryos. Therefore, cell shape changes likely contributing to intestine elongation are dependent on muscle contractions.

*Speaker

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06 Genetic control of acetylcholine receptor biosynthesis: from *C. elegans* to human diseases.

Genetic control of acetylcholine receptor biosynthesis: from C. elegans to human diseases.

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Abstract

Acetylcholine receptors (AChRs) are ion channels that support neurotransmission at the neuromuscular junction and have a neuromodulatory function in the central nervous system. Dysfunction of these receptors is linked to several pathologies, including myasthenia, schizophrenia, and epilepsy. The number of receptors present at the plasma membrane is thus finely tuned and results from a balance between biosynthesis, recycling, and degradation. Jean-Louis Bessereau's team uses *C. elegans* and its powerful genetic tools to identify new factors that control AChR biogenesis. Recently, the team performed a large-scale genetic screen that led to the identification of the *tmed-3* gene as a regulator of AChR biosynthesis. TMED-3 inactivation causes a decrease in AChR levels at the neuromuscular junction. TMED-3 is the ortholog of human *TMED7*and is involved in the ER-Golgi transition through interaction with the COPII proteins. To test whether misexpressed AChRs in TMED-3 mutants correlate with pathological conditions, I performed functional characterization of *TMED7* missense variants found in undiagnosed patients. After data mining for *TMED7* polymorphisms found in RD-Connect databases, I introduced the same variants into the *C. elegans*genome to test their effect on AChRs and their potential pathogenicity. Two out of the four variants tested cause a strong decrease in AChRs levels. The 2 missense mutations are carried by the same patient in compound heterozygous configuration, strongly suggesting that they could be at the origin of this patient's diseases.

Keywords: Acetylcholine receptors, TMEDs, C.elegans

*Speaker

07 LSM-8 is required for dynamic regulation of gene expression and is implicated in fertility and developmental pace of *C. elegans*.

LSM-8 is required for dynamic regulation of gene expression and is implicated in fertility and developmental pace of C. elegans

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Abstract

In eukaryotic genomes, heterochromatin correlates with silencing of genes. Regulation of gene expression and more particularly of gene silencing through heterochromatin is critical for the maintenance of developmental pathways and for ensuring appropriate responses to environmental stimuli. For years, heterochromatin has been considered as an inert and transcriptionally inactive structure.
Recently however, our lab identified the LSM2-8 complex as a key player in a pathway of post-transcriptional silencing of heterochromatin. We have found that the LSM2-8 complex promotes the selective degradation of transcripts arising from heterochromatic loci bearing H3K27me3, through the exoribonuclease XRN-2. This LSM2-8-mediated silencing of H3K27me3-bound regions defines a new mechanism for selective RNA degradation, and a previously unknown level of regulation for facultative heterochromatin in animals.

Here we show that this post-transcriptional silencing pathway is essential for proper development and that worms lacking a functional LSM2-8 complex display several phenotypes such as sterility and developmental delay.

To better characterize these phenotypes, we took advantage of the Auxin Inducible Degradation (AID) system to conditionally deplete the LSM-8 protein in a temporal and tissue specific manner.
Overall, we were able to recapitulate phenotypes seen in LSM-8 knock out mutants by conditionally depleting the LSM-8 protein with the AID system and get previously inaccessible temporal & tissue specific information, such as the requirement of LSM-8 in somatic but not in germline cells for fertility.

Keywords: heterochromatin, facultative, silencing, RNA, degradation, sterility, development, delay, LSM8

*Speaker

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08 *Caenorhabditis elegans* as an in vivo model system for investigating the congenital long QT syndrome type 2 pathogenic variants.

Caenorhabditis elegans as an in vivo model system for investigating the congenital long QT syndrome type 2 pathogenic variants

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Abstract

The congenital long QT syndrome (LQTS) stands as inherited cardiac channelopathy leading to a risk of sudden cardiac death in children and young adults. This channelopathy is part of a large superfamily of "conformational diseases" for which pathological variants cause protein misfolding but also affect channel function. *KCNH2* encodes the voltage-dependent potassium channel Kv11.1 (hERG), responsible for a major current of ventricular repolarization. 40% of LQTS (LQTS type 2) are caused by genetic variants in *KCNH2* leading to loss-of-function (LOF) of the Kv11.1 (hERG). Modelling the pathological variants is crucial to gain insight on the molecular mechanism underlying pathogenicity and identify potential therapeutic targets. The most commonly *in vitro* (e.g., oocytes of *X. laevis*, HEK 293 cells, induced pluripotent stem cell-derived cardiomyocytes) and *in vivo* (e.g., mice, rabbits) models present various limitations.
We propose to take advantage of *C. elegans* as an *in vivo* model system for LQTS type 2. UNC-103, the *C. elegans* homolog of Kv11.1/hERG, exhibits high conservation of functional domains (e.g., pore-forming region: 61% identity and 77% similarity). Furthermore, most Kv11.1 (hERG) regulators are also conserved in *C. elegans*.

To validate *C. elegans* as a functional model to readily analyse Kv11.1/UNC-103 variants, we selected 6 *KCNH2* missense variants responsible for LQTS type 2 in humans. These variants, well-characterized *in vitro* , are classified according to the mechanism leading to Kv11.1 (hERG) LOF: class 2 - defective trafficking (4 variants), class 3 - defective gating (1 variant), and class 4 - ion selectivity defective (1 variant).
By using a fluorophore tagged UNC-103 reporter strain (wrmSC::unc-103), we localized UNC-103 at the neuronal-muscular junction (NMJ) through to cholinergic presynaptic and postsynaptic markers (P*AChR*::Cla-1 BFP and unc-29 GFP) and in vulvar muscles. In the context of wrmSC::unc-103, we inserted the 6 variants using the CRISPR/Cas9 gene editing method. We quantified the impact of a class 2 variant trafficking at the NMJ and observed a significant decrease in the UNC-103 in this region. Functionally, the most straightforward phenotype is detected on the unlaid eggs. For all selected variants we detect fewer retained eggs in accordance with a hyperexcitability of the vulvar muscles implicated in the eggs laying

*Speaker

Exploring Neuronal Mechanisms and Therapeutic Strategies in GNAO1-Related Encephalopathies: Insights from C. elegans Studies

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Abstract

Dominant mutations in the *GNAO1* gene underlie a severe neurological condition characterized by hyperkinetic movement disorders, epilepsy, developmental delay, and cognitive decline, with infantile/childhood onset. *GNAO1* encodes the α-subunit of an inhibitory G-protein regulating ion channel activity, neurotransmitter release, and neurodevelopment. The pathogenic mechanisms underlying *GNAO1*-related disorders remain largely elusive and to date there are no effective therapies. Here, we generated CRISPR/Cas9-engineered *C. elegans* strains harboring five pathogenic variants in *goa-1*, the *C. elegans* orthologue of *GNAO1*, associated with diverse clinical features. Like null mutants, homozygous knock-in animals showed increased egg laying and were hypersensitive to aldicarb, an inhibitor of acetylcholinesterase, suggesting excessive neurotransmitter release by different classes of motor neurons (MNs) (HSNs and ventral cord MNs, respectively). Automated locomotion analysis of *goa-1* mutants revealed increased speed and number of body bends per minute, elevated reversal rates, and uncoordinated locomotion. Phenotypic profiling of heterozygous nematodes revealed a mutation- and cell-specific dominant-negative behavior of the mutant alleles. While the role of HSN neurons in inducing egg laying is well known, the specific class of neurons involved in the other phenotypes remains unclear. To address this issue, we performed RNAi knockdown of *goa-1* specifically in cholinergic, GABAergic, dopaminergic, and glutamatergic neurons. Our results demonstrate the involvement of all four neuronal classes in the hyperactive reversal behavior. Interestingly, animals exhibited hypersensitivity to aldicarb following *goa-1*(RNAi) in both cholinergic and GABAergic neurons, indicating an unpredicted role of Go in GABA neurons. In a pilot drug screening performed with compounds targeting G-protein coupled receptors (GPCRs), caffeine and istradefylline, an FDA-approved drug in the treatment of Parkinson's disease, were found to rescue the hyperactive motor behavior of *goa-1* mutants, by blocking, at least in part, a putative adenosine

*Speaker

10 Exploration of raw-milk cheeses' biological activity on oxidative processes and mobility using the in vivo model *Caenorhabditis elegans*.

Exploration of raw-milk cheeses' biological activity on oxidative processes and mobility using the in vivo model Caenorhabditis elegans

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Abstract

Raw-milk cheeses are fermented foods highly rich in microorganisms that can be considered as natural bioreactors. They could therefore represent a potential and innovative source of bioactive microbial metabolites with beneficial effects for health (both animal and human). In a prior study *in vivo* on the model *Caenorhabditis elegans* (*C. elegans*), we showed beneficial effects of fractions of goat raw-milk cheese against oxidative processes (1), highly implicated in aging and degenerative conditions affecting mobility thus impacting autonomy in aging individuals.

Currently, we evaluate the biological activity of seven selected raw milk cheeses from various cheese-making processes (animals involved and/or manufacturing techniques). Using *C. elegans*, we assessed their impact on oxidative processes and mobility disorders (mobility ensured in this model by its muscle fibers). Regarding their impact on oxidative processes, our findings indicate that the seven cheeses significantly enhance the survival rate of *C. elegans* by up to 6 times when exposed to an oxidative environment ($p < 0.05$). They were able to reduce the accumulation *in vivo* of radical species under oxidative conditions by up to -70% ($p < 0.05$) thus protecting *C. elegans* from oxidative damage. We showed activation of at least two defense metabolic pathways ($p < 0.05$) in response to oxidative medium. Concerning mobility, our study demonstrates that all raw milk cheeses preserve the integrity of the *C. elegans* muscle fibers during aging ($p < 0.0001$). In addition to protecting muscle fibers from degradation over time, these results suggest that raw milk cheeses preserve the movement abilities of *C. elegans* over time.

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*Speaker

Studying the dynamics of neuromuscular junction proteins

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Abstract

The neuromuscular junction in *C. elegans* consists of alternating excitatory (cholinergic) and inhibitory (GABAergic) synapses along nerve cords. Muscle cells thus receive two types of afferences and must localize the different neurotransmitter receptors in front of the corresponding presynaptic boutons to insure correct neurotransmission. At the level of the muscle cell membrane, two types of cholinergic receptors (N-AChRs and L-AchRs) and one type of GABAergic receptors (GABAARs) are clustered by specific intracellular and extracellular scaffolds. N-AChRs are the ortholog of a7 nicotinic receptors in mammals and are formed by a homo-pentamer of ACR-16 subunits. L-AChRs possess three a subunits (LEV-8/ACR-8, UNC-38 and UNC-63) and two non-a subunits (LEV-1 and UNC-29) and are sensitive to levamisole, an anthelmintic drug. These clusters of receptors are then localized by different extracellular synaptic organisers: Punctin/MADD-4 and CLE-1. Punctin is the ortholog of ADAMTSL3, a glycoprotein that belongs to the ADAMTS-like family. CLE-1 is the ortholog of collagens XV/XVIII, two multiplexin collagens that form a triple helix of collagen as well as possess heparan and/or chondroitin sulfate chains.
To better understand how these proteins are organised and interact together over time, it is essential to determine their dynamics. To do so, I have recently performed Fluorescence Recovery After Photobleaching (FRAP) on the three types of receptors, Punctin and CLE-1 using knock-in strains. I have also performed photoconversion to follow the renewal rate of Punctin.

FRAP experiments showed that extracellular matrix proteins are very stable at the neuromuscular junction, with very little recovery within the hour after photobleaching. These results suggest that Punctin and CLE-1 could establish very strong interactions within the extracellular matrix of the synapse that may limit their diffusion in the extracellular space. In contrast, the receptors showed recovery within the first 15 min after photobleaching. This recovery then reached a plateau, highlighting the presence of both mobile and immobile fractions of receptors. The different receptors showed specific rates of recovery and mobile fractions.

Finally, photoconversion of Punctin in *C. elegans* larvae showed that there is a complete renewal of Punctin after 24h. We are currently building knock-in strains with photoconvertible proteins tagged to each of our protein of interest in order to systematically follow the population of photoconverted and non-photoconverted proteins at *C. elegans* neuromuscular junctions.

*Speaker

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Impact of C.elegans' gut microbiota composition on its host

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Abstract

Recent studies have shown that *C. elegans* hosts a complex gut microbiota containing several γ-proteobacteria and Bacteroidetes, similar to the human microbiota (Dirksen et al., 2016). In our study, we use the CeMBio community (Dirksen et al., 2020), a simplified natural microbiota composed of a community of twelve bacterial strains, easily cultivated and capable of colonizing the nematode gut.
Numerous studies have demonstrated a direct link between the state of the microbiota and the health of the host (eg : dysbiosis of the microbiota linked with several diseases). However, when these studies are conducted *in vivo*, they require to work on complex organisms, that can show many constraints, such as ethical restrictions.

Thanks to its ease and low cost of culture, short life cycle, transparency, and no ethical restrictions, *C. elegans* is an organism of choice for establishing well-characterized and controllable microbiota of different compositions. Thus, it makes it a model of choice to pursue the understanding around the relationship between microbiota composition and its host's health.

As the CeMBio community has been established recently, not a lot of data are available about the characteristics of these microbiota strains and on how they can impact some physiological parameters of *C.elegans*.

Therefore, based on the CeMBio community, we have established "simplified microbiota", with different compositions and levels of complexity, in order to understand how this may impact worms' longevity, fertility, development, pathogen resistance and behavior. In parallel, we are also seeking to characterize these "simplified microbiota", by determining the level of colonization of the bacterial strains inside the gut and their ecological niches within

*Speaker

13 Marker-free sorting of *C. elegans* embryos at different ages and physiological states with FACS.

Marker-free sorting of C. elegans embryos at different ages and physiological states with FACS

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Abstract

FACS was used to collect large populations of staged fixed and live *C. elegans* embryos, as well as to select mutant larvae among a mixed population by using fluorescent markers. Native optical properties such as autofluorescence and light scatter parameters can often distinct populations without relying on markers transgenes or antibodies. For example, autofluorescence in C. elegans is predictive of lifespan, aging or survival after treatment in adults. However, weather C. elegans embryos at different stages or physiological states can be distinguished and sorted with FACS based solely on autofluorescence has not been reported. Here we took advantage of imaging flow cytometry and machine learning to develop a robust marker-free strategy for staging live wild-type *C. elegans* embryos using just a combination of physical and autofluorescence parameters. These can then be used to sort wild-type *C. elegans* embryos at any developmental stage with standard FACS. Furthermore we showed that, in parallel to embryo age, autofluorescence can also distinguish embryos of different maternal ages which are phenotypically different throughout their life, showing that it is possible to distinguish and sort individual live embryos at different physiological states in a marker-free manner.

Keywords: marker, free, FACS sorting, machine learning, embryo development

*Speaker

14 Characterization of Microtubule Binding Domains in Katanin unveils the essential role of its regulatory subunit (p80) for Microtubule severing activity.

Characterization of Microtubule Binding Domains in Katanin unveils the essential role of its regulatory subunit (p80) for Microtubule severing activity

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Abstract

Microtubule-severing enzymes (MSEs) Katanin, Spastin, and Fidgetin play essential roles in cell division and neurogenesis. They damage the microtubule (MT) lattice, which can either destroy or amplify the MT cytoskeleton, depending on the cellular context. However, little is known about how they interact with their substrates. We have identified the MicroTubule-Binding Domains (MTBD) required for Katanin function in C. elegans. Katanin is a h etero-hexamer of dimers containing a catalytic subunit p60 and a regulatory subunit p80, both of which are essential for female meiotic spindle assembly. Here we report that p80-like(MEI-2) dictates Katanin binding to MTs via two MTBDs composed of basic patches. Substituting these patches reduces Katanin binding to MTs, compromising its function in female meiotic-spindle assembly. Structural alignments of p80-like(MEI-2) with p80s from different species revealed that the MTBDs are evolutionarily conserved, even if the specific amino-acids involved vary, revealing a new type of motif involved in MT-interaction. In addition, our findings highlight the critical importance of the regulatory subunit (p80) in providing MT-binding to the Katanin complex, leading to optimal MT-severing activity.

Keywords: high throughput, lethality assay, Caenorhabditis elegans

*Speaker

15 Decrease of muscle activity induces axonal overgrowth in the SAB motor neurons, through a mechanism dependant of neuropeptide and voltage-gated calcium channels.

Decrease of muscle activity induces axonal overgrowth in the SAB motor neurons, through a mechanism dependant of neuropeptide and voltage-gated calcium channels.

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Abstract

During neural development, the activity levels of post-synaptic targets play a significant role in shaping the morphological development of axons in certain contexts. Using *Caenorhabditis elegans* as a model organism, we investigated the activity-dependent morphological alterations in a distinct class of motor neurons located in the worm's head, known as the SAB neurons. A reduction in muscle activity during a critical developmental window results in abnormal axonal growth patterns for SAB neurons, characterized by either excessive elongation (looping) or branching events (sprouting).
Through a targeted genetic analysis, we identified mutations in three genes that significantly attenuated the observed overgrowth phenotype. The first gene, *egl-3*, encodes a proprotein convertase involved in neuropeptide processing. The remaining two genes, *egl-19* and *unc-36*, encode subunits of voltage-gated calcium channels.

Based on our results we propose the following model. During development, reduced muscle activity triggers the secretion of a retrograde signal that acts on SAB motor neurons. Subsequently, these neurons undergo heightened activation, leading to the opening of voltage-gated calcium channels and an influx of calcium ions into the intracellular environment. Elevated calcium concentrations then precipitate the aberrant overgrowth of SAB axons.

Keywords: axonal plasticity, SAB, neuropeptide, voltage, gated calcium channels, muscle, retrograde signal

*Speaker

Programmed-DNA elimination among Rhabditidae species

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Abstract

Programmed-DNA elimination is a process in which portions of the genome are physically eliminated in somatic nuclei, while the genome remains intact in the germline. This process was spotted in 1897 by Th. Boveri in Ascaris parasitic nematodes. Programmed-genome elimination is also found in other metazoans such as birds, lamprey, marsupials, insects... By chance, we discovered somatic DNA elimination in *Mesorhabditis belari* within the Rhabditidae family. In this species, we observed that programmed-DNA elimination occurs between 5 and 15 cell-stage embryos by simple cytological observations and later confirmed elimination with bioinformatic approaches (Rey.C & al. 2023). Among Rhabditidae species, the DNA elimination of nematode species is very poorly documented. We systematically observed the embryos of 44 Rhabditidae species to ask whether the case of *Mesorhabditis* and *Ascaris* nematodes in the nematode phylum are very rare or not. Surprisingly, we found PDE very often in this small subsest of species. Our result strongly suggests PDE is widespread in nematodes, with C. elegans constituting a notable exception.

Keywords: DNA elimination, evolution

*Speaker

sciencesconf.org:vermidi25:533161

17 *Caenorhabditis elegans*: a model organism to unravel the molecular targets dictating the anti-leukemic potency of EAPB02303, a member of the Imiqualines family.

Caenorhabditis elegans: a model organism to unravel the molecular targets dictating the anti-leukemic potency of EAPB02303, a member of the Imiqualines family.

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Abstract

Imiqualines, analogues of the immunomodulatory drug Imiquimod, are a family of low molecular weight compounds synthesized by our team and protected by international patents. We focused on the potency of EAPB02303, lead compound of the second-generation family of Imiqualine, against Acute Myeloid Leukemia (AML), a haematological malignancy characterized by an aberrant differentiation and uncontrolled proliferation of myeloid blasts.
We demonstrated that EAPB02303 potently inhibited the proliferation of AML cells, with IC50s as low as 5 nM, thus presenting a significantly higher efficacy than the parent compound Imiquimod, or the members of the first-generation of Imiqualines. Additionally, EAPB02303 significantly downregulated the expression of proteins downstream of Ras (ERK1/2 and their phosphorylated form) 48 hours post-treatment. Of note, the Ras-MAPK signalling pathway is aberrantly activated in AML and mutations in Ras family members drive oncogenesis by increasing cellular proliferation and survival in AML.

We then used *Caenorhabditis elegans* (*C. elegans)* as a screening model system to unravel the molecular targets of EAPB02303. Indeed, *C. elegans* is extensively used as a model organism to study complex molecular processes of tumorigenesis. Mutations in signalling cascades promoting cancer in humans are conserved in *C. elegans*, and are associated with well-established phenotypes like sterility, infertility, longevity and vulva-less or multivulva formation. These phenotypic changes of the worms are reflective of aberrant deregulation of these pathways, and their implication in tumorigenesis. *let-60* gene in *C. elegans,* an ortholog of mammalian *Ras*, regulates the formation of the vulva. *let-60* gain of function mutations lead to an abnormal proliferation of the vulval tissues in adult mutants, resulting in formation of vulval-like protrusions called "ectopic vulvas" (multivulva phenotype or "Muv"). We validated the potential targets of EAPB02303 that were revealed *in vitro* using AML cell lines in *let-60/Ras* mutant strains. We showed that EAPB02303 significantly reduced the

*Speaker

Fast and easy method to culture and obtain large populations of male nematodes.

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Abstract

Nematodes are easy to maintain in the laboratory, but generating large populations of worms is labour-intensive and time-consuming. In addition, obtaining large quantities of males is challenging due to the predominant hermaphroditic nature of *C. elegans*, making high-throughput experiments with *C. elegans* males particularly complex.
To address these limitations, we have developed cost-effective and efficient methods to (1) cultivate large, synchronised worm populations and (2) easily obtain substantial quantities of males.

We have introduced a plate-based culture method that facilitates the growth of large, synchronised worm populations using standard incubators found in most worm laboratories. In addition, we have introduced a simple filtration technique that provides significant male populations within an hour. After filtration, the worm population is over 90% adult males, with no adult hermaphrodites present as all contaminants are larvae and embryos.
The culture and filtration methods we have developed are easy to implement and require minimal investment in equipment and consumables beyond the standard resources already available in worm laboratories. Both methods can be applied to nematode species similar in size to *C. elegans*.

Keywords: reproduction, filtering, culture method, males

*Speaker

sciencesconf.org:vermidi25:531783

Control of synapse formation by novel extracellular interactions

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Abstract

The diversity and specificity of synapses rely upon core organizing Cell Adhesion Molecules (CAM) that regulate contact initiation, synapse formation, maturation, maintenance and functional plasticity. In *C.* elegans, we recently identified that the ACR-16 acetylcholine receptor, well characterized at neuromuscular junctions, is also present at neuron-to-neuron synapses along the ventral cord of worms. Using a fluorescent reporter of the ACR-16 acetylcholine receptor, we performed a visual screen upon random mutagenesis to identify mutants with altered ACR-16 containing neuron-to-neuron synapses in the ventral nerve cord. One mutant caught our attention because the ACR-16 acetylcholine receptor was no longer synaptic and appeared diffuse at the neuronal surface. This phenotype was consistent with a mutation in a core synaptic organizer. We identified the mutated gene, which encodes a member of the IgLON family: RIG-5. RIG-5 shows a strikingly specific localization at ACR-16 neuro-to-neuron synapses, as does ZIG-8, a known *in vitro* binding partner of RIG-5. Overall, our data show that we identified two novel synaptic molecules that form a bridge across neurons and control ACR-16 clustering. Interestingly, the IgLON family is associated with a wide spectrum of human neurodevelopmental, neuropsychiatric and neurologic disorders, and might control synaptogenesis in mammals.

Keywords: synapses, IgLON, extracellular interactions, acetylcholine receptors

*Speaker

sciencesconf.org:vermidi25:531915

Evolution and plasticity of Caenorhabditis egg-laying behaviour

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Abstract

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 differently to the same stimulus, underscoring the presence of genotype-by-environment interactions (GEI) in egg-laying behavior. For our forthcoming VerMidi 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.

Keywords: Egg laying behaviour, neural circuit, genotype by environnment interaction, Quantitative Trait Loci

*Speaker

sciencesconf.org:vermidi25:533705

Searching for new regulators at C. elegans synapses

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Abstract

ACR-16 is the Caenorhabditis elegans ortholog of the a7 nicotinic acetylcholine receptor in vertebrates. Although extensively studied at C. elegans neuromuscular junctions, our recent findings indicate its presence at neuron-to-neuron synapses. We have shown that two cell adhesion molecules of the Immunoglobulin superfamily, RIG-5 and ZIG-8, very specifically localize at ACR-16 synapses. These molecules, RIG-5 and ZIG-8, act as bridges between the pre- and postsynaptic neuronal membranes, exerting control over the synaptic localization of ACR-16. Synapse assembly and function relies on a sophisticated molecular architecture involving extra- and intracellular crosstalk. To identify the molecular partners of RIG-5 and ZIG-8, we ran a genetic screen based on ACR-16 localization, and retrieved 56 mutants. We identified an ortholog of a neurotrophic factor receptor, whose mutation impairs ACR-16 at neuron-to-neuron synapses, albeit in a slightly different manner from rig-5 and zig-8. Current work aims at characterizing whether this molecule is present at synapses and understanding its role in the intricate network governing synapse assembly and function.

Keywords: nicotinic acetylcholine receptor, synapse regulation

*Speaker

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Dissecting the molecular mechanism triggering timely mitotic entry

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Abstract

Mitosis is a fundamental process for generating multicellular organisms, tissue renewal and homeostasis. During development, both the orientation of the division plane and the timing of mitotic entry fundamentally influence the positioning of daughter cells and their organization into tissues. However, the mechanisms that control the timing of mitotic entry still need to be better understood. Entry into mitosis is triggered by the activation of a mitotic kinases cascade (Aurora A> Plk1> CyclinB-Cdk1) and the concomitant inactivation of protein phosphatases (PPases). Paramount in mitotic kinase cascade is the activation of the Aurora A kinase (AURKA), which lies at the top of the kinase cascade. AURKA, like other kinases, is activated by phosphorylation of a conserved residue (T288) in the activation segment, named T-loop. AURKA can autophosphorylate on a conserved residue in the T-loop, but this site is rapidly dephosphorylated by counteracting PPases in the G2 phase of the cell cycle. As dephosphorylation maintains AURKA in an inactive state, the crucial question arises as to how AURKA can overcome the repressive effect of PPases to drive mitotic commitment. Our results indicate that the intrinsically disordered protein Bora, once phosphorylated, activates non-phosphorylated AURKA, which can then phosphorylate Plk1 on its T-loop, activating the mitotic kinase cascade. Our findings reveal that a phosphorylated serine (S112) on Bora can substitute in trans for AURKA autophosphorylation on the T-loop (T288) to activate AURKA. These observations raise several questions that I am addressing during my PhD: How does phospho-Bora (structurally) bind and activate AURKA toward Plk1? How is this mitotic entry pathway regulated during development to ensure asynchronous mitotic entry in the early *C. elegans* embryo?

Keywords: Mitotic entry, Aurora A, Kinases

*Speaker

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SIN3 acts in distinct complexes to regulate the germline transcriptional program in C. elegans

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Abstract

The SIN3 transcriptional coregulator influences gene expression through multiple interactions that include histone deacetylases (HDACs). Haploinsufficiency and mutations in SIN3 are the underlying cause of Witteveen-Kolk syndrome and related intellectual disability (ID)/autism syndromes, emphasizing its key role in development. However, little is known about the diversity of its interactions and functions in developmental processes. Here we show that loss of SIN-3, the single SIN3 homologue in *Caenorhabditis elegans*, results in maternal effect sterility associated with deregulation of the germline transcriptome, including desilencing of X-linked genes. We identify at least two distinct SIN3 complexes containing specific HDACs, and show that they differentially contribute to fertility. Single cell smFISH reveals that in *sin-3* mutants, the X chromosome becomes re-expressed prematurely and in a stochastic manner in individual germ cells, suggesting a role for SIN-3 in its silencing. Furthermore, we identify histone residues whose acetylation increases in the absence of SIN3. Together, this work provides a powerful framework for the *in vivo* study of SIN3 and associated proteins.

Keywords: epigenetics, maternal effect sterility, histone acetylation

*Speaker

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Energetic costs of cellular and developmental processes: an ATP perspective

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Abstract

Embryos are dissipative, thermodynamically out-of-equilibrium systems that constantly burn energy to establish and maintain their spatial, chemical, physical organization and drive highly complex and integrated biological processes. ATP plays a central role in the energy metabolism of the cell, and more widely in a broad range of roles in biological systems, from energy bal- ance to signaling. Recent years have seen huge strides in the precise understanding of cellular metabolism and its dynamics during embryonic development. In contrast, and despite the cen- tral importance of ATP in the energy economy of the cell, we know strikingly little about ATP dynamics in living organisms. In particular, the relationships between ATP dynamics and integrated cellular functions such as cell division, transcription and translation, and the precise cellular geography of ATP production and consumption remain unclear. During em- bryonic development, these questions are of central importance to understand how energy is managed, especially in egg-laying animal species, in which embryos have to develop e↩ectively and eciently to a self-feeding organism starting form a fixed energy pool. Here, we propose to develop new tools to revisit the fundamental question of the dynamics of ATP consumption and its role in cell physiology. We expect our results will reveal working principles selected through evolution to robustly and optimally manage energy consumption during embryonic development.

Keywords: physical bioenergetics, ATP, biosensors, microfluidics, dioxygen availability

*Speaker

Creation of C. elegans strains expressing an anti-ALFA tag nanobody

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Abstract

Actin cytoskeleton plays a crucial role in cell differentiation and determination by shaping the cell's architecture. Mammals have six actin genes with four exclusively expressed in muscles and two ubiquitously expressed; and these genes are highly conserved across species, including in *C. elegans*. In humans, mutations in actin genes cause diseases such as actinopathies and myopathies. To grasp the complexity of these disorders, it is crucial to dissect the functions and expression patterns of each actin isotype. However, given the limitations of current actin labelling tools, there is a need for novel labelling methods allowing to access each actin gene individually. As a solution, our lab is currently labelling actin genes with an ALFA tag inserted at a non-disruptive locus (called Int'Act); and *act-1*ALFA and *act-2*ALFA transgenics have already been generated. In order to visualise the ALFA tag *in vivo*, we are developing new transgenic strains expressing a nanobody directed against the ALFA tag, coupled to a fluorophore.

Keywords: actin, nanobody, ALFA tag

*Speaker

sciencesconf.org:vermidi25:534820

Redefining the GABAergic transporter system using C. elegans

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[2]Mécanismes en sciences intégratives du vivant – Université Claude Bernard Lyon 1, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique – France

Abstract

Traditionally in *C. elegans*, 26 out of 302 neurons were identified as GABAergic based on the co-expression of three determinant proteins: 1) GAD/UNC-25, which synthesises GABA, 2) VGAT/UNC-47, a vesicular transporter that packages GABA into vesicles, and 3) GAT/SNF-11, a plasma membrane transporter that recaptures GABA. With improved anti-GABA immunostaining, 15 additional GABA-positive neurons have been identified. These neurons do not all coexpress GAD*/unc-25*, VGAT*/unc-47* and GAT*/snf-11*. More specifically, three pairs of neurons express none of those: **AVAs, AVBs, and AVJs**. How they synthesise, uptake or package GABA is still unclear.
We hypothesise that these neurons use other transporters for uptake and vesicular packaging of GABA. We aim at identifying them and to probe 53 putative amino acid transporters.

On one hand, we undertook to build an atlas of these amino acid transporters by generating transgenic lines using the fosmid-based reporter strategy. So far, transgenic lines have been generated for 33 genes and neuronal expression could be seen for 25 candidates. Among those 25 genes, 5 are expressed in at least one of our neurons of interest.
On the other hand, we asked if the null alleles of those 53 genes affect anti-GABA immunostaining. The mutation of either a membrane or a vesicular transporter should decrease or increase the staining, respectively. To this date, in 5 out of the 31 existing mutant strains the anti-GABA immunostaining is affected. Additionally, we are currently using the CRISPR/Cas9 technology to confirm those results and to generate null alleles for genes with no available mutant strains. Four knock-out mutant strains have been generated in the lab so far. As immunostaining does not allow visual screen, we also have generated a strain expressing a cytoplasmic pan-neuronal GABA sensor. This will enable us to directly assess in vivo changes in GABA levels.

Keywords: GABA, VGAT, GAT, GAD, transporters, immunostaining, GABA sensor, neurons, neurotransmission, inhibition, fosmid, CRISPR

*Speaker

sciencesconf.org:vermidi25:536030

Functional validation of KCNN variants causing NEDMAB and Zimmermann-Laband syndrome-3 by CRISPR/Cas9 gene editing in C. elegans

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Abstract

Small-conductance Ca2+-activated K+ channels, commonly known as SK channels, are encoded in humans by the KCNN gene family and are widely expressed in the brain. These channels are highly conserved among vertebrates and invertebrates, and they play a role in afterhyperpolarization following action potentials and regulate the firing frequency of neurons.
Recently, mutations in *kcnn2* and *kcnn3* have been associated with two rare diseases: **NEDMAB** (Neurodevelopmental Disorder With or Without Variable Movement or Behavioral Abnormalities) and **ZLS3** (Zimmermann-Laband Syndrome 3).
ZLS3 patients harbor missense mutations that increase SK3 channel activity. Conversely, NEDMAB patients carries missense mutations in SK2 that were shown to eliminate channel function by electrophysiological studies. These patients share characteristics such as motor and language developmental delays, intellectual disability, movement disorders, cerebellar ataxia, autistic features, and epilepsy.
To investigate the impact of patient-specific variants, we used CRISPR/Cas9 gene editing to introduce nine human mutations into the *C. elegans* orthologue, *kcnl-1*, that exhibits sequence similarities of more than 50% with KCNN2 and KCNN3. The KCNL-1 channel regulates the excitability of neurons and muscles within the worm's egg-laying system, which constitutes a well-established model circuit for studying neuronal excitability.

Keywords: CRISPR/Cas9, functional study, neurodevelopmental disorder, epilepsy, potassium channel

*Speaker

Periodic structural collagens increase the resilience of the extracellular matrix

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Abstract

In the C. elegans worm, the apical extracellular matrix (aECM), or cuticle, acts like an exoskeleton to maintain shape and enable muscle contractions. It is mainly composed of different collagens arranged in different layers. One specific class of collagens stands out: it forms periodic circumferential structures known as furrows. Mutants in these collagens lead to a disordered cuticle without furrows, and are therefore called furrowless mutants. We have previously shown that furrowless mutants have a constitutive immune response in the underlying epidermis and that their stiffness is different from wild-type worms. We therefore hypothesize that the epidermis is capable of probing the mechanical state of the aECM. We are currently developing a model describing the aECM as an elastic shell under pressure, with or without furrows, and designed tests to measure its resistance to stretching. The hydrostatic pressure inside the worms was modified by changing the osmolarity of the medium. The mechanical contribution of muscles was eliminated by using different muscle contracting or relaxing agents. We found that, when exposed to hypoosmotic shock and when their muscles are relaxed, furrowless mutants burst violently within minutes, while wild-type worms remained intact. By measuring the distance between furrows, we found that the aECM of a wild-type worm is stretched by up to 10% in hypoosmotic conditions. By modeling the worm as a thin elastic shell under pressure, we are able to infer the hydrostatic pressure inside the worm from force-indentation curves. As expected, low external osmolarities lead to higher hydrostatic pressure induced by osmotic shock, due to the water influx towards the interior of the cuticle. We found that furrowless mutants have a higher hydrostatic pressure than wild-type worms. By using the Van't Hoff law to establish a relationship between external osmolarity and internal pressure in the worms, we are currently testing different saline conditions in which wild-type worms have the same pressure as furrowless worms. We hypothesize that the absence of periodic furrows in the mutant decreases the stretching capacity of the cuticle which leads to rupture when increasing the internal pressure. Our comprehensive mechanical characterisation of the worm skin will provide further insight into the dual role of periodic furrows: enhancing the matrix's resilience and serving as damage sensors.

Keywords: Extracellular matrix, Solid mechanics, Hydrostatic pressure, Atomic force microscopy

*Speaker

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Role of molecular chaperones in stress resilience of germ cells

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Abstract

Protein homeostasis (or proteostasis) is essential for cellular functions, which, in turn, supports the development and survival of the organism. An extensive network of proteostasis factors maintaining the correct folding, amounts, and localization of proteins have been well characterized in various systems and molecular chaperones hold a central role in the orchestration of these processes. In germ cells, proteostasis must be maintained as cytoplasmic proteins are inherited from oocytes to support early embryonic development after a lengthy pause in Meiosis I during gametogenesis. However, how the proteostasis network contributes to preserving the proteome of germ cells remains poorly understood. In this study, we are using the *Caenorhabditis elegans* model system to investigate the role of HSC70 (HSP-1 in *C. elegans*), a conserved chaperone important for the correct folding of many cytosolic and nuclear substrates, in the proteostasis and stress resilience of female germ cells. Using CRISPR/Cas9 gene editing to fluorescently label HSP-1 at the endogenous locus, we found that it relocalizes to the nucleus and to dynamic cytoplasmic puncta in germ cells upon heat stress. These cytoplasmic structures colocalized with markers for stress granules (SGs), which are dynamic membraneless ribonucleoprotein (RNP) condensates that form under stress. Finally, knockdown of critical components of the HSC70 machinery delays the disassembly of the condensates during stress recovery. Altogether, these findings implicate HSC70 in the dynamics of SGs in the female germ cells of *C. elegans*.

Keywords: Stress Response, Germ cells, Stress Granules, Proteostasis, Chaperones

*Speaker

30 Mechanisms of nuclear pore complex disassembly by the mitotic Polo-like kinase 1 (PLK-1) in *C. elegans* embryos.

Mechanisms of nuclear pore complex disassembly by the mitotic Polo-like kinase 1 (PLK-1) in C. elegans embryos

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Abstract

The nuclear envelope, which protects and organizes the genome, is dismantled during mitosis. In the *Caenorhabditis elegans* zygote, nuclear envelope breakdown (NEBD) of the parental pronuclei is spatially and temporally regulated during mitosis to promote the unification of the maternal and paternal genomes. Nuclear pore complex (NPC) disassembly is a decisive step of NEBD, essential for nuclear permeabilization. By combining live imaging, biochemistry, and phosphoproteomics, we show that NPC disassembly is a stepwise process that involves Polo-like kinase 1 (PLK-1)–dependent and –independent steps. PLK-1 targets multiple NPC subcomplexes, including the cytoplasmic filaments, central channel, and inner ring. PLK-1 is recruited to and phosphorylates intrinsically disordered regions (IDRs) of several multivalent linker nucleoporins. Notably, although the phosphosites are not conserved between human and *C. elegans* nucleoporins, they are located in IDRs in both species. Our results suggest that targeting IDRs of multivalent linker nucleoporins is an evolutionarily conserved driver of NPC disassembly during mitosis.

Keywords: Nuclear Pore Complex, Polo, like kinase 1, Mitosis, Nuclear Envelope, C. elegans embryo

*Speaker

Effect of the nested gene configuration on transcriptional dynamics

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Abstract

Gene expression is affected not only by their specific regulatory sequences and epigenetic environment, but also transcription of neighbouring genes. The most striking case of gene arrangement is the opposite nested configuration, in which one gene is entirely located within the intron of another gene in opposite orientation. This arrangement, which represents 5% of *C. elegans* protein-coding genes, may induce interference between transcription of nested and host genes affecting their expression.

To test this hypothesis, we measure the dynamics of transcription of nested and host genes *in vivo* using two complementary approaches: the NRDE-3 method, which we recently developed in the team, labels the transcript by programming the Argonaute NRDE-3 to bind the sequence of interest; while the more established MS2 and PP7 methods modify the transcript to be recognized by fluorescently-labelled MCP and PCP proteins. We use the fluorescence intensity of the transcripts accumulated at the active transcription site as a readout of the transcriptional activity of the locus.

As a first step, we used scRNA-seq data to find candidate gene pairs where nested and host genes are coexpressed in the same cells at the same time. We are currently confirming coexpression using smFISH. We aim now at measuring transcriptional dynamics *in vivo* of both genes at the same time to determine whether nested and host influence each other.

Keywords: Transcriptional regulation, live imaging

*Speaker

New players in the maintenance of germline/soma distinction

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Abstract

Sexual reproduction requires the production of functional gametes, a process that relies on the proper distinction between germline and soma and which depends on the regulation of specific gene repertoires. Our lab identified the zinc-finger transcription factor LSL-1 as a general transcriptional regulator of the germline program in *C. elegans*. *lsl-1* is expressed in germ cells from the birth of the P4 blastomere to the end of meiotic prophase I in the adult germline and it acts as a major transcriptional activator of germline genes involved in many aspects of the germline. LSL-1 activates transcription of genes involved in various important germline processes such as germ cell development and fate specification (e.g., *xnd-1*), P-granule composition (e.g. *pie-1*), mitosis-meiosis transition (e.g. *glp-1*), pairing and synapsis (e.g. *syp-2*) and genome stability (e.g. *dsb-2*) (Rodriguez-Crespo et *al.* 2022). *lsl-1* mutant germ cells fail to progress normally through meiotic prophase and exhibit somatic reprogramming, indicating that LSL-1 is also required for germ cell fate maintenance. LSL-1 functions by antagonizing the activity of HPL-2/HP1 and LET-418/Mi2, two heterochromatin-associated proteins that are known to repress ectopic expression of germline genes in the soma (Erdelyi et *al.* 2017, Ahringer and Gasser, 2018). Altogether, LSL-1 is a major regulator of the germline transcriptional program, that genetically interacts with other players in the germline/soma distinction process.

To better understand how LSL-1 activates the transcription at the molecular level, we searched for LSL-1 interactors. Co-IP-MS revealed the protein BRA-2 as a strong interactor of LSL-1. BRA-2 is homolog to the human ZMYND11 protein, which is predicted to be linked with histone methylation and transcription elongation regulation. *bra-2* mutants show phenotypic similarities with *lsl-1* mutants, e.g. sterility and meiotic defects. Additional candidates include three chromatin-associated proteins, XND-1, HIM-17 and MRG-1. All three proteins exhibit meiotic functions; however, XND-1 also functions as a germ cell determinant and MRG-1 is a barrier to germ cell fate reprogramming. Interestingly, MRG-1 is also a reader of histone mark H3K36 methylation, which is part of the germline epigenetic memory.

Finally, ongoing genetic interaction studies will allow us to determine whether LSL-1 and its interactors are functionally related. By these means, we aim to determine the molecular mechanisms by which LSL-1 regulate germline development and germ cell fate maintenance.

Keywords: germline, transcription, chromatin

*Speaker

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