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Sander van den Heuvel
Coordinating cell proliferation and differentiation during development

Molly Godfrey 1, Aniek van der Vaart 1, Ruben Schmidt 1, Lars-Eric Fielmich 1, Vincent Portegijs 1, Sander van den Heuvel 1

1 Developmental Biology, Padualaan 8, Utrecht University, 3584 CH Utrecht, The Netherlands

Animal development and tissue maintenance depend on the generation of specialized cells at the right place and in the proper numbers. To understand the regulatory mechanisms behind these processes, we study the coordination between cell proliferation and differentiation in the nematode Caenorhabditis elegans. We have combined a focus on the regulation of asymmetric cell division and arrest of cell proliferation during terminal differentiation, with efforts to expand the toolbox of technologies available for C. elegans studies. Recently added techniques include the use of light-induced protein interaction, which we applied to reveal how LIN-5 NuMA controls the position of the mitotic spindle and plane of cell cleavage (eLife, 2018). Another important direction is the use of lineage-specific genetics, based on conditional alleles of endogenous genes. We have applied this strategy to follow up on our previous discovery that SWI/SNF chromatin remodeling complexes contribute to arrest cell division during muscle differentiation (Cell, 2015). Ongoing studies of lineage-specific partial or complete SWI/SNF subunits loss, as well as double gene knockout and transcriptome analysis, will be presented at the meeting.
Session 1
PHR proteins form atypical SCF ubiquitin ligase complexes to ubiquitinate and degrade substrates

Muriel Desbois *, Karla Opperman 1, Oliver Crawley 1, Brock Grill 1

1 Scripps Research Institute – United States

PHR (PAM/Highwire/RPM-1) proteins are conserved RING E3 ubiquitin ligases that function in developmental processes, such as axon termination and synapse formation, as well as axon degeneration. In the past 5 years, using a combination of in vitro biochemistry in HEK293 cells and in vivo biochemistry from C. elegans, we deciphered the biochemical basis for how C. elegans RPM-1 and human PAM/MYCBP2 form noncanonical Skp/Cullin/F box (SCF) complexes. Our results indicate the atypical PAM SCF complex contains the F-box protein FBXO45 and SKP1, but lacks the Cullin CUL1. We showed this complex assembles by direct binding between PAM and FBXO45. Furthermore, we show that NMNAT2, an important axon protective protein, is recruited by FBXO45 into the PAM/FBXO45/SKP1 ubiquitin ligase complex. PAM then polyubiquitinates NMNAT2 which results in degradation by the proteasome. Unexpectedly, SKP1 functions as an auxiliary substrate recognition component to facilitate recruitment of NMNAT2 into this ubiquitin ligase complex. This insight into the biochemistry of ubiquitin ligase complexes formed by PHR proteins allowed us to design a point mutant for RPM-1 that acts as "biochemical trap" for ubiquitination substrates. We deployed this RPM-1 ubiquitination "trap" in affinity purification proteomics using C. elegans. Our results have identified several new putative RPM-1 ubiquitination substrates, including a kinase with prominent roles in the nervous system. Preliminary genetic experiments in worms indicate that this kinase is inhibited by RPM-1 in the nervous system. At present, we have three main aims for the project: 1) Expand our genetic analysis in C. elegans on RPM-1 and this kinase. 2) Determine how RPM-1 affects the stability of this kinase in the nervous system in vivo using CRISPR/Cas9 to tag the endogenous kinase with mScarlet. 3) Establish whether PAM, the human ortholog of RPM-1, binds and degrades this kinase in human cells and whether it affects the stability of the kinase in the human neuronal cell line SH-SY5Y.

*Speaker
Regulation of Katanin, an AAA+ Microtubule-Severing Enzyme essential for early embryogenesis in C. elegans

Nicolas Joly *† 1,2, Eva Beaumale 2, Lucie Van Hove 2, Lionel Pintard 2

1 Institut Jacques Monod (IJM) – Université Paris Diderot - Paris 7, Centre National de la Recherche Scientifique : UMR7592 – Cell Cycle and Development Team Université Paris Diderot, Bât. Buffon, 15 rue Hélène Brion, 75205 Paris cédex 13, France
2 Cell Cycle and development Team, CNRS-UMR7592, Institut Jacques Monod, Paris, France. – IJM – France

Microtubules (MTs) are dynamic cytoskeletal polymers with instrumental functions in cell division, morphogenesis, motility and signaling. MTs constantly polymerize and shrink and this dynamic behavior is regulated by a large family of MT-associated proteins (MAPs).

Whereas most of these MAPs interact with the microtubule plus or minus ends, another class interacts with the lattice of MT to sever them along their length, thereby controlling MTs size and density. Three evolutionarily conserved AAA+ (ATPase Associated with diverse cellular Activities) MT-severing enzymes have been identified: Fidgetin, Spastin and Katanin. Mutations of these enzymes have been linked to various defects and pathologies including developmental defects, neurodegenerative disorders such as hereditary spastic paraplegia (HSP), Fidget disease, prostate cancer and male sterility. However, the mode of action and the regulation of these enzymes is still poorly understood.

To have a better understanding of the role of these enzymes and of their regulation, we are using the nematode C. elegans. In this system, Katanin, which is composed of MEI-1 and MEI-2 subunits, is essential for the assembly of the acentrosomal female meiotic spindle but must be rapidly inactivated after meiosis to permit the assembly of the mitotic spindle that takes in the same cytoplasm place 20 min after. MEI-1 is subjected to post-translational modifications, in particular multisite phosphorylation and ubiquitination, but how these modifications modulate Katanin activity in space and time during the meiosis-to-mitosis transition remains poorly understood.

To decipher the exact role of MEI-1 multisite phosphorylation, we have developed a pipeline combining biochemistry, genetic analysis and live-imaging allowing us to show that MEI-1 phosphorylation not only regulates its stability but also its activity.

* Speaker
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A V0-ATPase-dependent apical trafficking pathway maintains the polarity of the intestinal absorptive membrane.

Aurélien Bidaud-Meynard *, Ophélie Nicolle 1, Markus Heck 1, Grégoire Michaux† 1

1 Institut de Génétique et Développement de Rennes (IGDR) – CNRS : UMR6290 – France

Intestine function relies on the strong polarity of intestinal epithelial cells and the array of microvilli forming a brush border at their luminal pole. Combining genetic RNAi screen and in vivo super-resolution imaging in the C. elegans intestine, we uncovered that the V0 sector of the V-ATPase (V0-ATPase) controls a late apical trafficking step through RAB-11+ endosomes necessary to maintain the polarized localization of both apical polarity modules and brush border proteins. We also show that the V0-ATPase genetically interacts with glycosphingolipids in enterocyte polarity maintenance. Finally, we demonstrate that silencing of the V0-ATPase fully recapitulates the severe structural, polarity and trafficking defects observed in enterocytes from patients with Microvillus inclusion disease (MVID), which suggests that it could be involved in the aetiology of this disorder. Hence, we describe a new function for the V0-ATPase in apical trafficking and epithelial polarity maintenance and the promising use of C. elegans intestine as an in vivo model to better understand the molecular mechanisms of rare genetic enteropathies.
Functional characterization of a nonaspanin at the inhibitory neuromuscular junction of Caenorhabditis elegans.

Marine Gueydan *,† 1, Bérangère Pinan-Lucarré 1, Xin Zhou 2, Maëlle Jospin 3, Aurore-Cécile Valfort 3, Floriane Gilles 2, Jean-Louis Bessereau‡ 4

1 Institut Neuromyogène - CNRS UMR 5310 - INSERM U1217 (INMG) – Institut Neuromyogène – Faculté de Médecine et de Pharmacie - 8 Avenue Rockefeller 69008 Lyon, France
2 Institut Neuromyogène - CNRS UMR 5310 - INSERM U1217 (INMG) – Institut Neuromyogène – France
3 Institut NeuroMyoGène CNRS INSERM – Université Claude Bernard - Lyon I – France
4 Institut Neuromyogène - CNRS UMR 5310 - INSERM U1217 (INMG) – Institut Neuromyogène – Université Claude Bernard Lyon 1 - 16 rue Raphaël Dubois 69100 Villeurbanne, France

To identify novel genes and mechanisms involved in the formation and regulation of inhibitory synapses, we used the inhibitory GABAergic neuromuscular junction of the nematode C. elegans as a genetically tractable model. After random mutagenesis of a knock-in strain expressing fluorescently tagged GABAA receptors (GABAAR), we screened for mutants with abnormal fluorescence pattern in vivo. We analyzed 36 mutant strains using a novel whole-genome sequencing strategy to simultaneously map and identify causative mutation without any prior time-consuming genetic mapping.

We undertook the functional characterization of a non-characterized gene, tentatively named nsp-3, which encodes an evolutionarily conserved transmembrane protein. nsp-3 deletion using CRISPR technology causes ectopic localization of GABAAR in intracellular compartments of the muscle cell. We found partial colocalization of these ectopic receptors with endosomal markers. Blocking lysosome biogenesis induces the accumulation of ectopic GABAARs in vacuolar structures. These data suggest that ectopic receptors are en route towards lysosomal degradation in nsp-3 mutants. Interestingly, we observed a 50 % decrease of GABAAR at synapses while we saw no change in GABA neurotransmission by electrophysiology. These and additional data predict the presence of a subsynaptic pool of GABAARs, which is depleted in the absence of NSP-3.

Using CRISPR/Cas9 to build a transcriptional reporter of the endogenous nsp-3 expression, we detected expression in most tissues. Rescue experiments showed that NSP-3 functions in muscles. We are currently investigating NSP-3 subcellular localization and its role in GABAAR trafficking and localization. Our data should identify novel functions of the nonaspanins in the traffic of neurotransmitter receptors in the nervous system.

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‡Corresponding author: jean-louis.bessereau@univ-lyon1.fr
CNRS UMS3421: a CRISPR platform for C. elegans research in France

Maïté Carre-Pierrat * 1

1 CNRS UMS3421 – CNRS : UMS3421 – France

The platform UMS3421 was created in 2011 to host, distribute and use the Mos insertion strains to perform transgenesis on demand. Since 2013 and the growing success of the CRISPR technologies, Mos techniques have been gradually abandoned and the UMS3421 activity has fully switched to CRISPR/Cas9 genome editing. We present here the services proposed by the UMS and some observations about the comparative efficiency of the main protocols published so far. Thanks to the support of the CNRS and University Claude Bernard Lyon 1, the UMS is providing a competitive service to the C. elegans researchers in France. How this service can be maintained in the future must be discussed by the C. elegans research community.
Session 2
Inter-individual variability in neuronal stress creates phenotypic variability

Laetitia Chauve *, 1, Catalina Vallejos 2,3,4,5, Sharlene Murdoch 1, Pia Todtenhaupt 1, Janna Hastings 1, Laura Biggins 1, John Marioni 3,6, Olivia Casanueva† 1

1 The Babraham Institute – United Kingdom
2 The Alan Turing Institute – United Kingdom
3 European Bioinformatics Institute [Hinxton] (EMBL-EBI) – United Kingdom
4 MRC Biostatistics unit – United Kingdom
5 UCL Department of Statistical Science – United Kingdom
6 Cancer Research UK – United Kingdom

Despite being isogenic and grown under controlled conditions, C. elegans populations exhibit widespread inter-individual variability in many traits. This makes C. elegans a relevant model to investigate non-genetic influences on phenotypic diversity. Several genetic pathways control C. elegans lifespan, generally converging on regulating metabolic genes and heat shock proteins (hsp), known to maintain protein-folding homeostasis. Studies monitoring transcriptional hsp reporters have shown that, despite being essential, hsp induction is highly variable across stress-exposed worms. This has consequences, as hsp expression in single-worm is predictive of genetic mutations buffering, lifespan and subsequent resistance to stress (Rea et al., 2005; Casanueva et al., 2011). However, much less is known about the variability of hsp or metabolic transcripts under unperturbed conditions. To study transcriptional variability at the single-worm level under basal conditions and for many transcripts simultaneously, we have developed a high-throughput quantitative PCR method and incorporated a Bayesian statistical approach to accurately quantify inter-individual variability in the expression of hundreds of genes. This method identified several inducible hsp as highly variable even in the absence of exogenous stress. Single molecule RNA Fluorescent In Situ Hybridization revealed that expression of these hsp under unperturbed conditions stems mostly from neurons. Using a bipartite reporter system GAL4/UAS (Wang et al., 2017) for hsp-16.41, we were able to confirm in vivo that hsp-16.41 expression in neurons at basal, is variable across worms. Our screen also identified several highly variable metabolic transcripts, including the intestinal fatty acid desaturase enzyme fat-7, responsible for fatty acid de novo synthesis and intestinal fat accumulation. Surprisingly, the highly variable hsp transcripts were anti-correlated with fat-7. To test if there was a causal relationship between hsp expression in neurons and fat-7 regulation in the intestine, we used transgenic lines over-expressing an upstream transcriptional regulator of chaperones (hsf-1) in neurons (N-HSF-1). We found that N-HSF-1 animals not only mount stronger stress responses but also have reduced fat-7 expression in the intestine and consequently exhibit decreased fat content. We have verified this inverse relationship in vivo, using a reporter for a stress inducible gene (N-HSP) and determined that heterogeneity in the expression of this reporter is associated

*Speaker
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with differences in stress resistance and also with *fat-7* expression levels and fat content. We have found that the activity of cyclic nucleotide gated channel *tax-2/tax-4*, expressed in specific sensory neurons is key to neuronal modulation of fat in the intestine. Some of the *tax-2/4* expressing neurons also express a TGF-beta/BMP ligand, which is known to modulate fat storages in the intestine (Clark *et al*. 2018). We find that neuronal stress negatively regulates TGF-beta/BMP expression and activity, suggesting that it is a key signal involved in the communication between neurons and the intestine. We are now testing how the variability of neuronal stress can, by modulating a dose-sensitive ligand, create metabolic heterogeneity within a population of genetically identical worms, perhaps providing a bet hedging strategy for survival.
A natural transdifferentiation event involving a mitosis is empowered by integrating signalling inputs with conserved plasticity factors.

Christelle Gally *, Claudia Riva , Martina Hajduskova , Sophie Jarriault

* IGBMC – CNRS UMR 7104, Inserm U 964, UdS – France

Transdifferentiation is the direct conversion of one differentiated cell type into another, with or without cell division. A natural transdifferentiation in C. elegans has been characterised by our lab in which the Y rectal cell transdifferentiates into the PDA motoneuron in the absence of cell division, with high efficiency, robustness and irreversibly (Jarriault et al., 2008). We have demonstrated that pluripotency-associated factors and chromatin modifiers are key to initiate Y-to-PDA transdifferentiation (Richard et al., 2011; Kagias et al., 2012) or to confer it robustness (Zuryn et al., 2014).

In order to further characterise the core cellular and molecular principles common to all transdifferentiations, we examined other potential natural reprogramming events in the worm. Our data point to the existence of a "plasticity cassette" involving sem-4/Sall4, sox-2, ceh-6/Oct4 and important for all transdifferentiations. We next focused on one such transdifferentiation, the formation of the DVB neuron from the K rectal cell. Since this event involves a cell division, we explored the role of transdifferentiation factors, the impact of the division, and their relationship.

We found that K division is asymmetric and necessary for DVB formation. This asymmetric division involves the Wnt pathway. However, proper asymmetric cell division, while required, is not sufficient for K-to-DVB transformation. Members of the core transdifferentiation cassette, and sem-4/Sall4 in particular, are required downstream of the division. Our data point to a model where two parallel and independent mechanisms, involving Wnt and a core plasticity cassette, are at play to erase K initial rectal identity, in addition to a Wnt-dependant activation of the specific terminal selector re-directing the cell to adopt a precise neuronal subtype identity.

*Speaker
The C. elegans SET-2/SET1 histone methyltransferase maintains germline cell fate by X-linked gene silencing and repression of TGF beta signaling components

Valérie Robert *,† 1, Andrew Kekupa’a Knutson 2, Andreas Rechtsteiner 2, Gaël Yvert 1, Susan Strome 2, Francesca Palladino‡ 1

1 Laboratoire de Biologie et Modélisation de la cellule (LBMC) – CNRS : UMR5239 – France
2 MCD Biology UCSC – United States

Chromatin factors contribute to germline maintenance by preserving the germ-cell-specific transcriptional program. In the absence of the conserved histone H3 Lys4 (H3K4) methyltransferase SET-2/SET1, C. elegans germ cells progressively lose their identity over generations, leading to sterility. How this transgenerational loss of fertility results from the absence of SET-2 is unknown. To address this question, we performed expression profiling across generations on germlines from mutant animals lacking SET-2 activity. We found that gene deregulation occurred in 2 steps: initially as a priming step in early generations, and progressing to loss of fertility in later generations. By performing Within-Class Analysis, we extracted genes whose deregulation in set-2 mutant germlines contribute to sterility. Further analysis of these genes identified X-chromosome desilencing and derepression of TGF beta signaling components as priming events in loss of germline identity. Altogether, our findings reveal that SET-2/SET1 represses multiple conserved transcriptional and signaling programs incompatible with germ-cell fate.

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‡Corresponding author: francesca.palladino@ens-lyon.fr
Heterochromatic foci and transcriptional repression by an unstructured MET-2/SETDB1 co-factor LIN-65

Stephen Methot *, 1, Colin Delaney 1, Micol Guidi 1, Iskra Katic 1, Susan Gasser† 1, Jan Padeken 1

1 Friedrich Miescher Institute for Biomedical Research (FMI) – Switzerland

The segregation of the genome into accessible euchromatin and histone H3K9-methylated heterochromatin helps silence repetitive elements and tissue-specific genes. In Caenorhabditis elegans, MET-2 the homolog of mammalian SETDB1 catalyzes H3K9me1 and me2, yet like SETDB1, its regulation is enigmatic. Contrary to the cytosolic enrichment of overexpressed MET-2, we show that endogenous MET-2 is nuclear throughout development, forming perinuclear foci in a cell cycle-dependent manner. Mass spectrometry identified two co-factors that bind MET-2: LIN-65, a highly unstructured protein, and ARLE-14, a conserved GTPase effector. All three factors colocalize in heterochromatic foci. Ablation of lin-65, but not arle-14, mislocalizes and destabilizes MET-2, resulting in decreased H3K9 dimethylation, dispersion of heterochromatic foci and derepression of MET-2 targets. Mutation of met-2 or lin-65 also disrupts the perinuclear anchoring of genomic heterochromatin. Loss of LIN-65, like that of MET-2, compromises temperature stress resistance and germline integrity, which are both linked to promiscuous repeat transcription and gene expression.

*Speaker
†Corresponding author: susan.gasser@fmi.ch
Males as somatic investment in the parthenogen nematode Mesorhabditis belari

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We report the novel reproductive strategy of the nematode Mesorhabditis belari. This species produces only 9% of males, whose sperm is necessary to fertilize and activate the eggs. However, the majority of fertilized eggs develop without using the sperm DNA and produce female individuals. Only in 9% of eggs is the male DNA utilized, to produce sons. We found that mixing of parental genomes only give rise to males because the Y-bearing sperm of males is much more competent than the X-bearing sperm to penetrate the eggs. In this remarkable strategy,
asexual females produce few sexual males whose genes never re-enter the female pool. Here, production of males is of interest only if sons are more likely to mate with their sisters. Using game theory, we show that in this context, the production of 9% of males by *M. belari* females is an evolutionary stable strategy.
Session 3
C. elegans wild populations harbor natural genetic variation in non-genetic inheritance phenomena

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While heredity mostly relies on the transmission of DNA sequence, additional molecular and cellular features are heritable across several generations. According to theoretical predictions, the transgenerational memory of non-DNA based information could be of particular importance in the adaptation of living organisms to varying environments [1]. The main purpose of our work is to test whether and how non-genetic inheritance systems are modulated by natural genetic variation.

In the nematode Caenorhabditis elegans, insights into such unconventional inheritance result from two lines of work. First, the mortal germ line (Mrt) phenotype was defined as a multigenerational phenotype whereby a selfing lineage becomes sterile after several generations, implying multigenerational memory [2, 3]. Second, certain RNA interference (RNAi) effects are heritable over several generations in the absence of the initial trigger [4-6]. Both lines of work converged as the subset of heat-sensitive Mrt (tsMrt) mutants closely correspond to mutants defective in the RNAi-inheritance machinery [7-10].

Here we report the first pieces of evidence that C. elegans natural populations harbour natural genetic variation in a multigenerational phenotype. Indeed, we found that several C. elegans wild isolates display a tsMrt phenotype in laboratory conditions. In order to pinpoint the molecular inheritance system underlying this multigenerational phenotype, we focused on determining the genetic bases of the quantitative variation among the C. elegans wild isolates, using both laboratory crosses and association mapping. We found the main causal polymorphism between two isolates (MY10, JU1395) to be an indel in the set-24 gene, encoding a SET- and SPK-domain protein [11]. Using 95 C. elegans wild isolates, we found a strong association of the tsMrt phenotype with a non-synonymous polymorphism in the morc-1 gene.

Interestingly, in C. elegans, morc-1 is required for RNAi inheritance and its knockout causes a tsMrt phenotype [12] suggesting that the natural genetic variation in the tsMrt phenotype could correspond to natural variation in non-genetic inheritance involving RNAi inheritance. To verify this hypothesis, we inserted a germline-expressed GFP transgene [13] in five wild isolates. We demonstrated that wild isolates display different durations of RNAi memory. Using the same GFP transgene, we are currently testing the impact of the natural non-synonymous polymorphism in morc-1 on RNAi inheritance.

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We concluded that *C. elegans* natural populations harbour natural genetic variation in epigenetic inheritance which provides an exciting model to experimentally test the importance of epigenetic inheritance systems in the adaptation of living organisms to varying environments.

Natural molecular variant enhancing \emph{C. elegans} dauer induction in response to diverse environmental cues

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Virtually all organisms possess the capacity to flexibly adjust their development in response to environmental changes. A prime example of such adaptive developmental plasticity is dauer formation in the nematode \emph{C. elegans} whereby larvae can adopt an alternative, stress-resistant larval stage (termed dauer) in response to harsh environmental conditions, such as high population density, starvation, or high temperature. Here we characterized a \emph{C. elegans} isolate (JU751, France), which shows an unusually strong propensity to form dauers in response to diverse, mildly adverse environmental conditions, including high temperature and relatively low population densities. Performing a QTL analysis, we identified a region on chromosome III associated with variation in dauer induction. After NIL construction and further restriction of the target region, we focused on a single candidate variant, a 90bp deletion in the presumptive promoter region of \textit{eak-3}. \textit{eak-3} is a gene known to inhibit dauer induction, seemingly by regulating the synthesis or secretion of dafachronic acid (DA). Using CRISPR-Cas9 gene editing, we demonstrate that this 90bp deletion, leading to likely complete loss of \textit{eak-3} expression, represents the causal molecular change underlying the evolution of increased dauer induction in JU751. We further present experimental evidence that this variant can potentially provide a short-term benefit in populations undergoing bouts of acute stress, such as high temperatures, similar to the ones encountered in the natural habitat. Our result connects with classical developmental genetic studies to allow for precise identification of evolutionary changes in well-characterized signalling networks regulating adaptive developmental plasticity.

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Why are genetically identical individuals growing in the same environment phenotypically different?

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Genetically identical individuals growing in the same environment often show substantial phenotypic variation. The reasons for this phenotypic variation are usually unknown. I previously found that isogenic *C. elegans* growing in the same environment differ in developmental speed, including the relative developmental rate of the soma and the germline (soma-germline heterochrony), fecundity and many other fitness important traits such as size and resistance to early starvation. We found maternal age to be the major determinant of this phenotypic variation in with progeny of young mothers being surprisingly impaired in size, developmental speed, starvation resistance and fecundity, and they also show different soma-germline heterochrony. Changes in maternal provisioning of yolk to the embryo, which increases with age, explain many of these phenotypic differences but do not explain differences in soma-germline heterochrony and fecundity. I now have evidence showing that these differences are induced in the offspring by exposure to pheromone in the parents.

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Lactobacillus rhamnosus Lcr35® as an effective treatment for preventing Candida albicans infection in the preclinical model Caenorhabditis elegans

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The increased recurrence of Candida albicans infections is associated with greater resistance to antifungal drugs. This involves the establishment of alternative therapeutic protocols such as the use of probiotic microorganisms whose antifungal potential has already been demonstrated using preclinical models (cell cultures, laboratory animals) and clinical studies. Understanding the mechanisms of action of probiotic microorganisms has become a strategic need for the development of new therapeutics for humans. In this study, we investigated the prophylactic antifungal properties of Lactobacillus rhamnosus Lcr35® using the in vivo Caenorhabditis elegans model. On the top of having a pro-longevity activity in the nematode, Lcr35® protects the animal from the fungal infection even if the yeast is still detectable in its intestine. At the mechanistic level, we note the repression of genes of the p38 MAPK signaling pathway and genes involved in the antifungal response induced by Lcr35® suggesting that the pathogen no longer appears to be detected by the worm immune system. However, the DAF-16 / FOXO transcription factor, implicated in the longevity and antipathogenic response of C. elegans, is activated by Lcr35®. These results suggest that the probiotic strain acts by stimulating its host via DAF-16, but also by suppressing the virulence of the pathogen. An exhaustive study of the C. elegans transcriptome will be carried out in order to decipher the mechanisms of action of Lcr35®.

*Speaker
Exploring fungal virulence using C. elegans

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In the laboratory, we use the interaction between C. elegans and the nematophagous fungi Drechmeria coniospora as a model system to investigate fungal pathogenesis and the host response to infection. Our aim for this project is to characterise fungal virulence factors and thus understand fungal pathogenesis in an in vivo setting. During infection, D. coniospora secretes a broad range of proteins into the host. In order to study the effect of these potential virulence factors, we designed a strategy to express the corresponding genes directly in C. elegans under the control of an epidermal promoter (using a CRISPR-Cas9-based method). One class of factors that we are interested in are heat-labile enterotoxins. There are a very large number of genes encoding these bacterially derived toxins in the D. coniospora genome. We wish to determine their mode of action. Another gene is predicted to encode a novel transcriptional repressor. Worms that express these fungal virulence factors are sick and short-lived, making the generation of transgenic strains problematic. In order to counterbalance the toxicity of such proteins, we tried using RNAi to suppress expression of the virulence genes. As this was not efficient, we are now applying the auxin inducible degron system to degrade the corresponding proteins in a controllable way. This will allow us to modulate tightly the expression of the fungal proteins and facilitate future functional studies.

Related publication:


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Posters
Intestinal mitochondrial activity modulates epidermal innate immunity

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Several genes identified in an RNAi screen for targets that modulate C. elegans’s response to epidermal fungal infection encode mitochondrial proteins (1). Knockdown of these genes ubiquitously, or specifically in the intestine, suppresses the epidermal expression of the antimicrobial peptide gene, nlp-29, after Drechmeria coniospora infection. This suppression, best characterised for the knockdown of the mitochondrial inner membrane protein, SPG-7, has been found to be independent of the mitochondrial UPR transcription factor, atfs-1, thus pointing to a role for mitochondrial activity per se in regulating nlp-29 expression.

We aim to uncover the mechanistic basis of this mitochondrial-dependent cross-tissue signaling via an unbiased F2 clonal EMS screen. We have constructed the strain that will be mutagenized. It carries an nlp-29p::GFP construct, with a gain of function mutation for gpa-12 that activates reporter gene expression in adults, in an rde-1(ne300) mutant background, with specific rescue in the intestine:

frIs30[(col-19p::GPA-12gf)]; pNP21(pBunc-53::GFP)] I; frSi17[pNP160(mtl-2p::RDE-1;3rde-1 ttTi5605)] II; frIs7[nlp-29p::GFP, col-12p::DsRed] IV; rde-1(ne300) V

When this strain is put on spg-7(RNAi), nlp-29p::GFP expression is suppressed. We aim to identify F3 populations carrying mutations which relieve this suppression and restore normal GFP expression in the adult epidermis. Progress on this screen will be reported.


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Adenylosuccinate Lyase deficiency in the recycling pathway is essential for developmental timing, germline maintenance and muscle integrity in C. elegans.

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The purine biosynthesis pathway is a metabolic network conserved from prokaryotes to humans, ensuring ATP and GTP homeostasis. Purines can either be synthesized de novo, reused, or produced by interconversion of extant metabolites using the so-called recycling pathway. Moreover, intermediates can act as signal metabolites regulating gene expression. This pathway is well characterized in microorganisms, but little is known about its regulation in metazoans. Different diseases are associated with deficiencies in purine synthesis enzymes leading to neuromuscular defects, autistic spectrum behaviors and psychomotor delay in humans. We focused our analysis on the deficiency of Adenylosuccinate Lyase (ADSL), which is an enzyme involved in the purine de novo and the recycling pathways causing neuronal and muscular symptoms in patients.

To better understand mechanisms underlying this deficiency, we have established C. elegans as a metazoan model organism to study the purine biosynthesis pathway, specially the ADSL deficiency.

In our study, by sequence alignment, HPLC profiling and functional complementation in yeast, we have shown that both the de novo and the recycling pathway are functionally conserved in C. elegans.

Thanks to our study, we are able to ascribe developmental and tissue specific phenotypes to separable steps of the purine metabolism network in a metazoan model organism. Our analysis shows that ADSL activity in the recycling pathway plays a crucial role, in a tissue specific manner (for germline maintenance and for muscle integrity) and during the post-embryonic development.

*Speaker
Tools and resources for tissue-specific RNAi

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There are many situations when researchers want to knock down a gene specifically in one tissue. In our work, we are interested in cross-tissue communication during stress responses (see Abstract by Claire Maynard). We previously used strains generated in other laboratories based on tissue-specific rescue of RNAi activity in an rde-1 mutant background. Others have shown that rde-1(ne219) is not a complete loss of function, so we have now created robust tissue specific RNAi strains in the null rde-1(ne300) background by single-copy insertion of rde-1 under the control of the col-62 (epidermis) or mtl-2 (intestine) promoter. The strains behave as expected, thus the intestine-specific RNAi strain shows developmental arrest on act-5(RNAi) while the epidermis-specific RNAi strain exhibits no phenotype. Conversely, bli-1(RNAi) and dpy-7(RNAi) only affect the epidermis-specific RNAi strain. Similarly, sta-2(RNAi) which targets the transcription factor responsible for epidermal anti-fungal defence strongly abrogates nlp-29 expression upon infection in the adult in the latter strain.

On another technological note, we have shifted plasmid construction from commercial seamless DNA cloning kits to SLiCE (Seamless Ligation Cloning Extract) cloning. As standard laboratory E. coli strains can be used as a source for the SLiCE extract, it is highly cost-effective and easily prepared (1). The creation of single-copy insertion by CRISPR/Cas9-based genome editing at defined MosSCI positions on chromosome I and II coupled with the SEC selection strategy is efficient and effective. We have made our collection of single insertion plasmids available at Addgene (https://www.addgene.org/Jonathan_Ewbank/) and hope that they will be of use to the community.

Thanks to Pranay Shah and Jonathan Ewbank for their contributions.

Regulation of nuclear position by microtubules and cortical tension ensures proper DNA segregation during late mitosis

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Coordinating mitotic spindle and cytokinetic furrow positions is essential to ensure proper DNA segregation. While signaling emanating from the mitotic spindle is known to be essential for furrow positioning, we previously showed that tight regulation of myosin is also required to coordinate furrow and spindle positions. During the first division of *C. elegans* embryos, abnormal accumulation of myosin at the anterior cortex induces a strong displacement of the furrow towards the anterior, thereby uncoupling cytokinetic furrow and spindle positions and leading to strong DNA segregation defects (Pacquelet et al.; J Cell Biol, 210, 1085). Here, we show that these DNA segregation defects are very surprisingly corrected at the end of mitosis. We found that this correction relies on the concomitant displacement of the furrow and of the anterior nucleus towards the posterior and anterior poles, respectively. It also coincides with an anteriorly directed flow of cytoplasmic particles. While microtubules contribute to nuclear displacement, relaxation of an excessive tension at the anterior cortex plays a central role in the correction process and simultaneously regulates cytoplasmic flow as well as nuclear and furrow displacements. This work thus reveals the existence of a so far undescribed correction mechanism, which relies both on microtubules and cortical tension to regulate nuclear position during late mitosis and ensure correct DNA segregation.

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Physical and functional interaction between SET1/COMPASS complex component CFP-1 and a Sin3S HDAC complex

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The CFP1 CXXC zinc finger protein targets the SET1/COMPASS complex to non-methylated CpG rich promoters to implement tri-methylation of histone H3 Lys4 (H3K4me3). Although H3K4me3 is widely associated with gene expression, the effects of CFP1 loss vary, suggesting additional chromatin factors contribute to context dependent effects. Using a proteomics approach, we identified CFP1 associated proteins and an unexpected direct link between C. elegans CFP-1 and an Rpd3/Sin3 small (SIN3S) histone deacetylase complex. We find that mutants of CFP-1, SIN-3, and the catalytic subunit SET-2/SET1 have similar defects, but cfp-1 mutant phenotypes are more severe. Transcriptional profiling of mutants revealed common misregulated genes and that CFP-1 has independent regulatory interactions with SET1/COMPASS and SIN3S. CFP-1 directly binds SIN-3 through a region including the conserved PAH1 domain and recruits SIN-3 and the HDA-1/HDAC subunit to H3K4me3 enriched promoters. Our results reveal a novel role for CFP-1 in mediating interaction between SET1/COMPASS and a Sin3S HDAC complex at promoters.

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Cellular response to Wnt signals: an in vitro approach using C. elegans embryonic cells

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Embryogenesis is controlled by secreted proteins called morphogen that signal at a distance through specific receptors present on the plasma membrane of target cells. One such well-studied morphogen is Wnt that signals through its receptor Frizzled across species. This signalling pathway is also important to maintain tissue homeostasis; in the adult, abnormality in this signalling can cause tumours and cancers. During C. elegans embryogenesis, Wnt signalling controls various asymmetric divisions along the antero-posterior axis. However, the interaction mechanism of morphogen with its receptors, leading to the cellular response of such target cells is still unknown. To understand these mechanisms, we use the primary culture of C. elegans embryonic cells and expose them to artificial Wnt gradients controlled by microfluidic devices. Using high-resolution imaging to visualize fluorescently tagged endogenous Frizzled on the membrane, we monitor the localization and dynamics of the receptor. This approach allows us to determine how Wnt ligands induce a cellular response through Frizzled at the single cell level which in turn can lead to asymmetric division. Until now beside setting up all the required techniques to carry the project, the heterogeneity and clustered distribution of Frizzled is identified and small but significant decrease in heterogeneity is observed upon exogenous Wnt treatment. In future, dynamics of Frizzled cluster by time-lapse movies and diffusion of single Frizzled molecules by FCS technique will be studied in 1. Uniform exogenous Wnt; 2. Graded Wnt concentration; 3. Coculture with Wnt expressing C. elegans cells & 4. Control i.e. without additional Wnt. At the end of this study, it will improve our understanding of Wnt signalling by filling up the knowledge gap about the distribution and dynamics of the Wnt receptor Frizzled upon Wnt signal.
In vivo study of the biological properties of cheese fractions

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Natural products have been the source of new drugs over the last 30 years (1). However less than 1% of the microbial biodiversity has been explored. In this context, the complex microorganisms diversity found in fermented food, especially cheese, represents a great interest as a source of new bioactive molecules. Some publications revealed in vitro anti-inflammatory activity of cheese extracts (2) as well as in vivo health benefit of cheese consumption in humans (3). The goal of this study is to identify molecular fractions isolated from cheese and having anti-oxidant and anti-inflammatory effects.

In order to investigate the anti-inflammatory potential of different cheese fractions, a bioguidage approach has been developed to isolate and identify new molecules. Goat cheese was chosen as a model for this cheese fractionation. The characterization of the biological properties of these cheese fractions are performed using the in vivo model C. elegans. The nematode survival in presence of the fractions in its food, is evaluated as well as its anti-oxidant capacity. Preliminary results are promising, suggesting a beneficial effect of 5 out of 9 fractions regarding C. elegans survival.

According to the data obtained in C. elegans, the interesting fractions will be used in a global transcriptomic study associated to in vitro tests to characterize the mechanism of action of the cheese fractions.

Related publications:
3. F. Sofi et al, Effects of a dairy product (pecorino cheese) naturally rich in cis-9, trans-11 conjugated linoleic acid on lipid, inflammatory and haemorheological variables: a dietary intervention study, Nutrition, Metabolism & Cardiovascular Diseases, 2010, 20, 117-124

*Speaker
The nematode *C. elegans* has emerged as an important animal model for drug discovery. Nevertheless, it has been thought to be a poor candidate for drug testing due to the relatively inefficient drug uptake caused, *inter alia*, by the impermeability of the cuticle to non-water-soluble compounds. To circumvent this obstacle, *CeleScreen* implements specific carriers for testing the effect of drugs by bringing them directly into *C. elegans*. This method favors the ingestion of almost all drugs, whatever the appetite of the nematode for each, and moreover, at lower dose compared to earlier trials. This is very important as it allows for assaying molecules at a more "physiological" condition. We have recently proved the concept by demonstrating that methotrexate (MTX), a potent teratogen, encapsulated into metal-organic frameworks (MOFs) was physiologically administrated into the worm resulting in severe teratogenesis effect. Analytical analysis showed that the effective dose of MTX needed is far less using our technology compared to conventional delivery method. We are currently testing the efficiency of our protocol with other drugs eliciting toxic effect on different worm phenotypes. To this end, *CeleScreen* develops 2 different business areas: 1/ Provide services for molecule toxicity screening or activity testing using our proven and patented technology; 2/ Offer solutions for 'on-demand projects' by developing *C. elegans*-based assays for outcome investigations, quantitative analysis and biochemical analysis.
MADD-4/Ce-Punctin processing defines synaptic identity at C. elegans neuromuscular junction

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In C. elegans, body-wall muscle cells receive both excitatory (cholinergic) and inhibitory (GABAergic) inputs. MADD-4/Ce-Punctin is an extracellular matrix protein, secreted by motoneurons, which specifies the type of receptors to cluster at each type of neuromuscular junction (NMJ). Indeed, two MADD-4 isoforms are differentially expressed at NMJs: a small isoform (MADD-4S) is expressed at both types of synapses whereas a long isoform (MADD-4L) is exclusively expressed by cholinergic motoneurons. While the long isoform is necessary for the correct localization of cholinergic (ACh) receptors in front of corresponding ACh terminals, the short isoform is required for the clustering of GABA receptors at inhibitory inputs. However, this model does not account for the fact that, in the absence of the long isoform, GABA receptors remain in front of GABA terminals, even though MADD-4S is expressed at cholinergic and GABAergic NMJs.

Recent evidence reveals that MADD-4S, but not MADD-4L, is cleaved and that N- and C-terminal fragments localize differentially at the synapse. Indeed, the N-terminal part of MADD-4S exclusively localizes at GABA sites, whereas the N-terminal part of MADD-4L is restricted to ACh synapses. Moreover, the C-terminal fragment, which is common to both isoforms, is enriched at cholinergic synapses. Undergoing experiments are on the way to specify the site of cleavage and protease involved, as well as the functional significance of MADD-4S processing.

In parallel, a genetic screen identifies neurexin-1 as a regulator of MADD-4 localization at the NMJ. In nrx-1 mutants, overall MADD-4 levels are unchanged but its pattern along the dorsal and ventral cords is disturbed. This phenotype is paralleled by an increase of GABA receptor levels, while ACh receptor levels remain unaffected.

*Speaker
Genetic regulation of a muscular potassium channel in C. elegans by the dystrophin complex

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The Dystrophin-Associated Protein Complex (DAPC) is a large protein complex that links the extracellular matrix to the actin cytoskeleton. On the extracellular side, the DAPC is attached to laminin through α-dystroglycan, which associate with the transmembrane protein β-dystroglycan. On the intracellular side, dystrophin interacts with syntrophin, dystrobrevin and other proteins that associate with the actin cytoskeleton (Balse and Eichel, 2017). In addition to its mechanical and structural functions, it has been shown that dystrophin regulates Nav1.5 voltage-gated sodium channel levels in mice cardiac muscle cells (Gavillet et al., 2015). Interestingly, we have found that dystrophin also regulates the membrane targeting and distribution of TWK-28, a muscular K2P channel in C. elegans.

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Two-pore domain potassium channels (K2P) form a large family of well-conserved ion channels that play a key role in the establishment and maintenance of the resting membrane potential of almost all animal cells. Despite the fundamental role of K2P channels, some very basic questions about their biology are still largely unexplored. In particular, we still know very little about the molecular and cellular processes that determine the number of active channels and their distribution at the cell surface in different cell types.

We have recently identified a key conserved amino acid that can be mutated to strongly increase the activity of vertebrate and invertebrate K2P channels (Ben Soussia et al, 2019). By inserting these mutations into the C. elegans twk-28 gene, we have been able to generate a strong gain-of-function mutant with a clear locomotor deficit, that was an ideal starting point for a genetic suppressor screen. In addition to dystrophin (dys-1), we found various other genes implicated in the regulation of TWK-28, remarkably all associated with the DAPC complex. Surprisingly, we found that mutations in these genes modify the distribution of TWK-28 channels at the muscle cell surface in different ways, but do not affect other K2P channels present in body wall muscles.
Therefore, we now wonder how the DAPC complex interacts specifically with TWK-28 and whether this interaction is direct or if other unknown factors are implicated. To answer these question, we plan to perform co-immunoprecipitation experiments and electrophysiological assays.

*Speaker
Spindle Size and Assembly Timing
Regulation by Microtubule Dynamics
During Early Embryonic Cleavages

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ABSTRACT:

During early embryonic development of metazoans, cells undergo rapid cleavages without expansion of the embryo inducing a reduction of cell size. The mitotic spindle is a macromolecular microtubule-based structure that ensures proper partitioning of chromosomes during cell division. As other organelles, the mitotic spindle has the ability to adapt its dimensions relative to reduction of cell size. The mechanisms underlying the dimensional and temporal scaling relationships between this dynamic structure and cell size remain unknown.

We recently observed in C. elegans nematode that the time required to assemble the mitotic structure was constant and independent of cell size in early embryos. By measuring microtubule dynamics, spindle size and cell volume during early embryonic development of the nematode C. elegans and the sea urchin P. lividus, we found that the growth rate of spindle microtubules is reduced during development and adapts to changes in cell volume. Using both experimental

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and theoretical approaches we explain how modulation of microtubule growth rate can trigger the adaptation of spindle length while maintaining spindle assembly constant as cell volume becomes smaller. Furthermore, using different experimental conditions and applying several perturbations to the microtubule network, we identified that all microtubule dynamics parameters are robustly linked and regulated in mitotic cells in order to maintain microtubule length and spindle length adapted to cell size. We propose that microtubule dynamics in cleaving embryos are tightly controlled and sensitive to cell volume. This regulation might be important to ensure faithful chromosome segregation during the rapid cleavages occurring during the early stages of life.
Polarised distribution of K2P channels in the body wall muscles of C. elegans

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Three distinct families of potassium-selective ion channels exist in the genomes of all animals. Among them, two-pore domain potassium (K2P) channels play a key role in the central and peripheral nervous system to control background leak currents responsible for establishing and maintaining the resting membrane potential. In C. elegans, 47 genes encode K2P channel subunits, but few of them have been studied in detail. Combining transcriptional reporter strains (CRISPR/Cas9-based knockins) and classical PCR fusion-based approaches (Hobert, 2002), we have found that nine K2P channel subunits are co-expressed in the body wall muscles of C. elegans. To understand if this co-expression is correlated with specific functional roles, we investigated the subcellular distribution of these channels by tagging them with fluorescent proteins (mNeonGreen, wrmScarlet, TagRFP-T, or TagBFP).

As anticipated, these channels (except one) are present at the cell surface. However, they do not distribute in a random or uniform fashion. We have found that channels can be restricted to the apical, apico-basal or baso-lateral compartment. Some are visible in muscle arms, others are not. In addition, and maybe most strikingly, the density of some channels varies along the antero-posterior axis. For example, TWK-28 is addressed at the anterior tip of each muscle cell, whereas TWK-24 is restricted to the middle section of the cell. In addition, we have found that other membrane proteins such as the BK channel SLO-1 or the neurotransmitter transporter SNF-6 also exhibit a similar asymmetric distribution.

To our knowledge, this has never been observed for any muscle-expressed protein in C. elegans. These highly specific subcellular distribution patterns raise a number of fascinating questions regarding the cellular mechanisms that compartmentalize membrane proteins in such a robust and intricate fashion. Gradients along the antero-posterior axis suggest that planar cell polarity pathways might be implicated. Our next experiments will thus be to study the canonical Wnt pathway, which is known to be implicated in cell polarity in C. elegans and many other organisms. We will also investigate the possible role of extracellular matrix components and major cell-organizers such as Ankyrin, Spectrin and the dystrophin associated protein complex.

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Characterization of the mechanisms of adaptation to levamisole

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At the neuromuscular junction, acetylcholine receptors (AChRs) mediate fast excitatory neurotransmission. In C. elegans, a class of AChRs is sensitive to the agonist levamisole. Prolonged exposure to levamisole induces irreversible worm paralysis. However, worms with mutations in genes involved in AChR biosynthesis or clustering are able to adapt to levamisole and recover their motility.

Detailed analysis demonstrated that all worms first become hypercontracted and paralyzed. Wild type animals then relaxed and remained paralyzed while adapting worms remained hypercontracted and started to move after few hours. Accordingly, calcium measurement revealed that in adapting mutants calcium concentrations remain high in body wall muscles all along levamisole exposure. Our research aims to decipher the mechanisms underlying this adaptation process and, in particular, to understand how muscle cells can remain functional when facing prolonged hypercontraction.

Our results indicate that elevated Ca2+ concentration in the muscle could activate the Ca2+-dependent phosphatase tax-6/Calcineurin, which then play a key role in the adaptation process. Muscle-specific degradation of TAX-6 before levamisole exposure prevents the adaption of mutants that normally adapt. TAX-6 could in turn activate different pathways including a CREB-dependent transcriptional response as mutation of crh-1, a CREB1 homolog, impairs adaptation. TAX-6 also seems to control the levels of AChRs at the membrane, which is reduced during adaptation. Finally, we observed that mitochondria become fragmented in the muscle of non-adapting worms while they remain fused in adapting worms.

Altogether these results suggest that muscle cells can be reprogrammed at different levels to overcome prolonged activation and contraction.

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K2P Atlas: a comprehensive study of these ion channels expression and hyperactivation

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Two-pore domain potassium channels (K2P) control neuronal excitability and play a central role in the establishment and maintenance of the resting membrane potential of almost all animal cells. In C. elegans, 47 genes encode K2P channel subunits, but only four have been studied so far. As a first step to better understand the biology of K2P channels in C. elegans, we have tried to classify them based on their expression pattern.

To do so, we have generated transcriptional reporter strains either by CRISPR/Cas9-based genome engineering or using a classical PCR fusion-based approach (Hobert, 2002), which consist in creating transgenic lines expressing a GFP fused to a promoter or intron fragment for each K2P. Observing over 30 K2P channels so far, we have found that they are expressed in muscles, neurons, motorneurons, hypodermis, HMC, pharynx muscles or the digestive tract. Most channels seem to be expressed only in a small number of cells or cell-types. Interestingly, we found that (1) twk-8, twk-12, twk-24, twk-18, twk-28 and twk-42 are almost exclusively expressed in body wall muscles; (2) twk-2, twk-9, twk-13, twk-16, twk-29, twk-35, twk-39 twk-48 mostly in motorneurons, and that (3) some K2Ps are expressed in multiple tissues.

In parallel, we have developed a systematic strategy to build gain-of-function mutants of K2P channels by CRISPR/Cas9-based gene editing (Ben Soussia et al, 2019). We have shown that vertebrate and invertebrate K2P channels can be hyperactivated simply by mutating a conserved residue in the second transmembrane domain (TM2.6), close to the channel pore. Based on our expression atlas, we targeted muscle- and motorneuron-expressed channels. We generated nine hyperactive TM2.6 mutants, and found that they caused strong locomotion defects consistent with the expression patterns of these genes. In doing so, we extend the complement of "Unc" mutants of C. elegans by targeted mutagenesis, and open the way to study the biology of K2P channels in vivo using forward genetic screens.

In conclusion, both of these approaches gave us to have a preliminary landscape for the biology of K2Ps, composed of their expression and function. This will allow us to prioritize our candidates for future studies, notably to perform in vivo knock in approaches and genetic screens.

*Speaker
Screen for new actors of muscle aging

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We previously showed that muscle aging is characterized by a dramatic decrease in the expression of genes encoding proteins required for muscle contraction, followed by a change in mitochondria morphology, and an increase in autophagosome number (Mergoud et al., 2017). To analyze further the mechanisms involved in muscle aging, we used CRISPR/Cas9 to generate a tnt-2::F2A::tagRFPt::PEST reporter strain in which tagRFPt expression reflects the expression of the troponin T. In this strain, body-wall muscle (BWM) fluorescence and tagRFPt protein level decrease with age.

Using this strain, positive regulators of muscle aging could be identified by looking for genes whose inactivation leads to a slower decrease of fluorescence during aging. We undertook a semi-clonal screen after EMS mutagenesis, looking at the F2 generation for brighter worms than controls at the same age.

Details of the screen and some preliminary results will be presented.

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Evolution of QR neuroblast migration and mig-1 regulation in C. elegans and other nematodes.

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In the first stage larva of Caenorhabditis elegans, the QR neuroblast migrates anteriorly, while undergoing three rounds of division. The two daughter cells of QR.pa, QR.paa and QR.pap (henceafter called QR.pax) acquire a neuronal fate and their final position can be scored by Nomarski microscopy. Mentink et al. (Dev Cell 2014) found that QR.pa cell migration stops upon expression of the Wnt receptor MIG-1, which surprisingly is not induced by positional clues but by a position-independent timing mechanism. We thus wondered 1) how robust the final QR.pax positioning was when confronted to stochastic noise and environmental variation and 2) how the final position and the underlying positioning mechanisms evolve.

We measured variation in the final position of the QR.pax in a set of C. elegans wild isolates in different environments. Preliminary results indicate significant natural variation in QR.pax position in C. elegans, yet in a relatively tight window. At higher temperature, QR.pax mean position is posteriorly shifted, while starvation immediately after hatching increases the variance in QR.pax position. Interestingly, we noticed that the variance of the final position is not higher than the variance of other embryonic migrating neurons. Measuring egg size of wild isolates and N2 mutants, we revealed that the difference in final position could be partially explained by the size at hatching. These results are consistent with an intrinsic time-based mechanism for the stop of the migration.

We further studied QR.pax position in different nematode species. In Caenorhabditis briggsae and C. tropicalis (the two other selfing species in the Caenorhabditis genus), the QR.pax cells are found in a similar position as in C. elegans. We aligned mig-1 putative cis-regulatory sequences in a large set of Caenorhabditis species (from http://caenorhabditis.org/, thanks to Mark Blaxter’s laboratory). The alignment revealed highly conserved motifs in the upstream sequence and the first intron, especially in the Elegans supergroup, with some occasional losses in a species (e.g. C. briggsae). These motifs could provide crucial information about the evolution of mig-1 regulation and QR neuroblast migration.

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Analysis of the role of the SIN-3/HDAC histone deacetylase complex in X-chromosome silencing in the germline of C. elegans

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Histone post-translational modifications are key players in genome organization, and control most DNA-related cellular processes, including genome stability, DNA replication and gene expression. In the germline of C. elegans, the silenced X-chromosome is hypoacetylated at lysine residues on histone H3 and H4 (Strome et al., 2014). The mechanisms responsible for this deacetylation, and its impact on X silencing remain unknown. I will present expression profiling data showing that X-linked genes are globally desilenced in the germline of animals carrying a mutation in sin-3, encoding the main subunit of the conserved SIN-3 histone deacetylase (HDAC) complex. My current project is to investigate the link between SIN-3/HDAC and X chromosome hypoacetylation and silencing. To this end, I am studying SIN-3 localization in the germline using a CRISPR-tagged allele, and using immunostaining to look at acetylation patterns on the X-chromosome in the germline of sin-3 mutants. My long term goal is to study the role of SIN-3/HDAC in establishing acetylation patterns on the X-chromosome, and to establish how these correlate with gene silencing on the X. In this poster, I will also present a novel protocol that we have developed to purify germline nuclei using FACS analysis, allowing us to probe chromatin profiles specifically in the germline.
How does Katanin interact with and sever microtubules and contribute to the assembly of female meiotic spindle in C. elegans embryo?

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Microtubules (MTs) are dynamic cytoskeletal polymers with instrumental functions in cell division, morphogenesis, motility and signaling. MTs undergo continual assembly and disassembly within the cell and this dynamic behavior is regulated by a large family of MT-associated proteins (MAPs), which control the polymerization-depolymerization rates. An additional class of proteins responsible for microtubule dynamics regulation, is the Microtubules Severing Enzymes (MSE). This family is composed of three enzymes: Spastin, Fidgetin and Katanin, which belong to the large family of AAA+ ATPases (ATPase Associated with diverse cellular Activities). MSE regulate microtubule length and density by severing the MT lattice. Mutation of these enzymes has been linked to various defects and pathologies, however, their mode of action and their regulation is still poorly understood.

The nematode C. elegans represents an attractive model to study MSE function and regulation using a combination of genetics, cell biology and biochemical approaches. All MSE are conserved in this system where they fulfill critical functions in cell division. In particular, Katanin, which is composed of MEI-1 and MEI-2 subunits, is essential for the assembly of the acentrosomal female meiotic spindle. MT severing might contribute to meiotic spindle assembly by generating more MT polymers from an inefficient chromatin-based MT nucleation process. Consistent with this hypothesis, it has been recently reported that MSE can amplify microtubule arrays through lattice GTP-tubulin incorporation (Vemu et al., Science 2008). More specifically, MSE introduce nanoscale damages along the microtubules which can be repaired by incorporation of GTP-tubulin allowing microtubules re-polymerization. How katanin primarily interacts with microtubules is however not understood. We showed previously that MEI-2 subunit provides MT binding to the Katanin complex in vitro (Joly et al., Development 2016) but the molecular determinants are however unknown. Using complementary biochemical and live-imaging approaches, we aim to decipher the precise role of MEI-2 and its contribution to Katanin function.


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Asymmetric cell division and the acto-myosin cytoskeleton in nematodes

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The first division of the Caenorhabditis elegans embryo is a classic example of asymmetric cell division. Much has been learned from this model concerning the role of the acto-myosin cortex in symmetry breaking and polarity establishment, and the role of astral microtubules in spindle positioning. Although they undergo similar asymmetric divisions, nematode embryos from other genera appear to be lacking key characteristics observed for Caenorhabditis, including cortex behavior. In this project, we will characterize the acto-myosin cytoskeleton in three nematode embryos evolutionarily distant from C. elegans, in order to understand how acto-myosin organization and dynamics is modified in embryos of non-Caenorhabditis genera.

We chose three species that showed interesting cortical activity and were sequenced: Oscheius tipulae, Pristionchus pacificus and Diploscapter pachys. D. pachys is particularly interesting, as this is a parthenogenetic species, so the sperm cue for cortical symmetry breaking is lacking. As a first step, since these species are not amenable to easy genetic manipulation like C. elegans, we performed phalloidin staining on fixed embryos to observe the actin network in these species. The embryos of O. tipulae and P. pacificus have enhanced cortical shape changes at the anterior pole of the embryo as observed by DIC microscopy. However, phalloidin staining showed that there did not appear to be an enhanced actin signal at the anterior pole, and that the asymmetry in cortical actin was similar in C. elegans, P. pacificus and O. tipulae. There were qualitative differences in the organization of cortical actin however, with P. pacificus and O. tipulae displaying more bundles and long-range structures, and more cytoplasmic actin in the case of O. tipulae.

Similar cortices were also observed with D. pachys, despite the fact that this species undergoes very little cortical shape change prior to division, as observed by DIC microscopy. In order to measure dynamics, we are introducing fluorescently-labeled actin probes into P. pacificus by transgenesis via bombardment, which has recently been successfully performed in P. pacificus, using an antibiotic selection marker. Furthermore, D. pachys has recently been reported to be sensitive to RNAi by feeding, so in parallel with our studies on P. pacificus, we will knock down genes involved in cortical dynamics in D. pachys, and observe the effect on polarity establishment and asymmetric division. We will also perform embryo permeabilization via perm-1 RNAi, thus allowing the entry of drugs and dyes into D. pachys embryos for further analysis.

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Understanding kinetic delays in biological systems

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Cascades of activation are defined by a succession of sequential activation of signaling proteins. This leads to the activation of a downstream effector, typically affecting a specific biological function with a precise intensity and timing. Here, we used the RhoA activation cascade as a model to analyse the unfolding of this cascade in a cell. In this cascade, we can measure, at a specific location of the cell cortex, a stereotypical delay between the activation of the upstream regulator and the recruitment and activation of the downstream effector. First, we proceeded to a careful characterization of the dynamics of the two sequential steps of the cascade. Using TIRF microscopy, we focused on the different steps of the RhoA activation cascade, using the Myosin as a landmark to measure the delay within the cascade at the cortex of C. elegans early embryos. Second, using single-molecule imaging, we focused on the last step of this cascade and measured the dynamic modulation of the binding (Kon) and the unbinding rate (Koff) of the Myosin. We then developed a simple numerical model that takes advantage of the dynamic measurements of Kon and Koff to predict the temporal evolution of this cascade. We propose that this simple and generic model – which can in essence fit any activation cascade – offers a simple mathematical framework to understand the temporal dynamics of signaling cascades, and the delay and change in the shape of the response which can be observed between the input and the output of a cascade.

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Dynein dynamics at the microtubule plus-end and the cortex reveal a posteriorly increased dynein engaging rate reflecting polarity in C. elegans embryos

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During asymmetric cell division, dynein generates pulling forces at the cortex, which position the spindle to reflect polarity and ensure correct daughter cell fates. In this instance, During asymmetric cell divisions, cortical dyneins generate forces essential to position the spindle after polarity cues, prescribing daughter cells fate. As member of dynein act as a member of the trimeric complex with GPR-1/2/LGN and LIN-5/NuMA. However, despite a measured force imbalance, no clear enrichment of dynein in posterior embryo half was detected in fixed C. elegans embryo, suggesting rather a transient cortical localization in agreement with anaphase rocking modelling. We used the nematode zygote and thus focused on the dynamics of dynein both in the cytoplasm and at the cortex. We found that dynein accumulates at the microtubule plus-ends, in a mechanism reminiscent of the one previously described in yeast and minimal systems. It indirectly hitch-hikes on EBP-2EB1 and similarly to this latter, is not transported. Interestingly, this accumulating contributed only modestly to cortical forces, suggesting that most of dynein reaches the cortex likely by diffusing in the cytoplasm. To relate dynein residency and forces generating, we tracked dynein at the cortex and found two populations, displaying directed and diffusive motion. The latter fraction revealed force generating events. Surprisingly, while we found that in the both mechanisms above, dynein cortical targeting is not polarized, diffusive tracks were more dense on the posterior tip of the embryos, where forces are higher. Since dynein resides equally long on both half-cortices, we propose that it is accounted by an increased dynein binding rate posteriorly. This extra density depended on GPR-1/2LGN. Since in csnk-1(RNAi), increased forces anteriorly coincided with an increased dynein density, we propose that increased dynein binding rate on posterior reflects polarity. This asymmetric (polarized) dynein–microtubule on-rate supplements the regulation of mitotic progression through the non-polarized detachment rate.

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A paternal side of the story: FNDC-1 contributes to paternal mitochondria elimination

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Maternal inheritance of mitochondrial DNA is considered a conserved and essential trait. In *C. elegans* paternal mitochondria elimination (PME) takes place following fertilization by selective autophagy in a quick and precise process. In the past years maternal factors that contribute to PME have been subject of study giving valuable information to understand this process, however, key factors are still missing and the mechanisms that restrict it to the elimination of sperm-derived organelles are not well understood.

FNDC-1, *C. elegans* ortholog of the mammalian FUNDC1, is a mitochondrial outer membrane receptor that is widely expressed in somatic tissues where it contributes to mitochondrial quality control following hypoxic stress. Here we report that FNDC-1 is also strongly expressed in sperm but not oocytes and that it contributes to PME during the first stages of embryonic development. We observed that paternal mitochondrial DNA is normally undetectable in wildtype larva while it can be detected in the cross-progeny of *fndc-1* loss of function mutant males. Moreover, loss of *fndc-1* delays paternal mitochondria degradation, but not that of membranous organelles, a nematode specific membrane compartment whose fusion is required for sperm motility. Thus, this is the first example of a paternal ubiquitin-independent mitophagy receptor playing a role in the selective degradation of sperm mitochondria.

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PAR-4/LKB1, a novel regulator of intestinal lumen morphogenesis?

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Intestinal epithelial cells can absorb food through their highly specialized apical surface, the so-called brush border, which is composed of many microvilli. Ectopic activation of the kinase and tumor suppressor PAR-4/LKB1 has been shown to be sufficient to induce complete polarization and formation of an apical brush border with microvilli-like structures in intestinal epithelial cancer cell lines. However, the function of PAR-4/LKB1 in intestinal cells has so far not been characterized in vivo. In order to determine whether it is involved in intestinal cell polarization and brush border formation, we used confocal and transmission electron microscopy to observe the intestinal epithelium in C. elegans par-4 thermosensitive mutant embryos. We have found that PAR-4/LKB1 loss-of-function has no effect on polarity establishment and maintenance in intestinal cells. However, it results in strong intestinal lumen defects such as an increase of lumen width and formation of abnormal apical membrane protrusions. Furthermore, we also observed that many par-4(it47) embryos present supernumerary apical junctions. Altogether, these results show that PAR-4/LKB1 is required for proper intestinal lumen morphology. Further experiments will help us to understand through which effectors PAR-4/LKB1 acts in order to play this role.

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Investigating the role of the Polo-Like Kinase-1 in Nuclear Pore Complex disassembly during mitosis

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Nuclear envelope breakdown (NEBD) is an essential step of mitosis ensuring proper chromosome segregation between the daughter cells. NEBD is triggered by conserved mitotic kinases notably Polo like kinase 1 (Plk1) and Cyclin dependent kinase 1 (Cdk1). The Polo-like kinase 1 (Plk1) is an evolutionarily conserved serine-threonine kinase that plays a key role at multiple stages of mitotic entry and progression. Plk1 activity must be tightly regulated, in space and time, as defect in Plk1 regulation has drastic consequences.

However, its precise role in mitotic entry and progression is not completely understood. We have shown recently that Plk1 is recruited to the nuclear envelope in prophase just prior to NEBD in both human cells and C. elegans embryos to promote NEBD. In C. elegans the nucleoporins NPP-1, NPP-4 and NPP-11, which form a trimeric complex located in the central channel of the nuclear pore, recruit Plk1 to trigger nuclear envelope breakdown (Martino et al, Dev. Cell, 2017). Once at the envelope, Plk1 probably phosphorylates structural nucleoporins to breach the permeability barrier and to dismantle the NPCs. PLK-1 critical targets at the nuclear envelope to trigger NEBD remain unidentified.

NPP-19 is a structural nucleoporin with a scaffolding role in the NPC interacting with several nucleoporins including NPP-22, NPP-13 and NPP-8. NPP-19 interacts with PLK-1 in Y2H and is required for timely asynchrnous division. Thus this project aims to understand Plk1 contribution to NPC disassembly by deciphering the contribution of Plk1’s phosphorylation of the nucleoporin NPP-19 using a combination of genetics, advanced live-cell imaging and biochemical approaches.

Overall this project aims to decipher the role and mechanism by which Plk1 promotes NEBD which will help us better understand the molecular mechanisms promoting NEBD and ensuring accurate chromosome segregation by the mitotic spindle.

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