EPIGENMED

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PROGRAMME D'EXCELLENCE I-SITE

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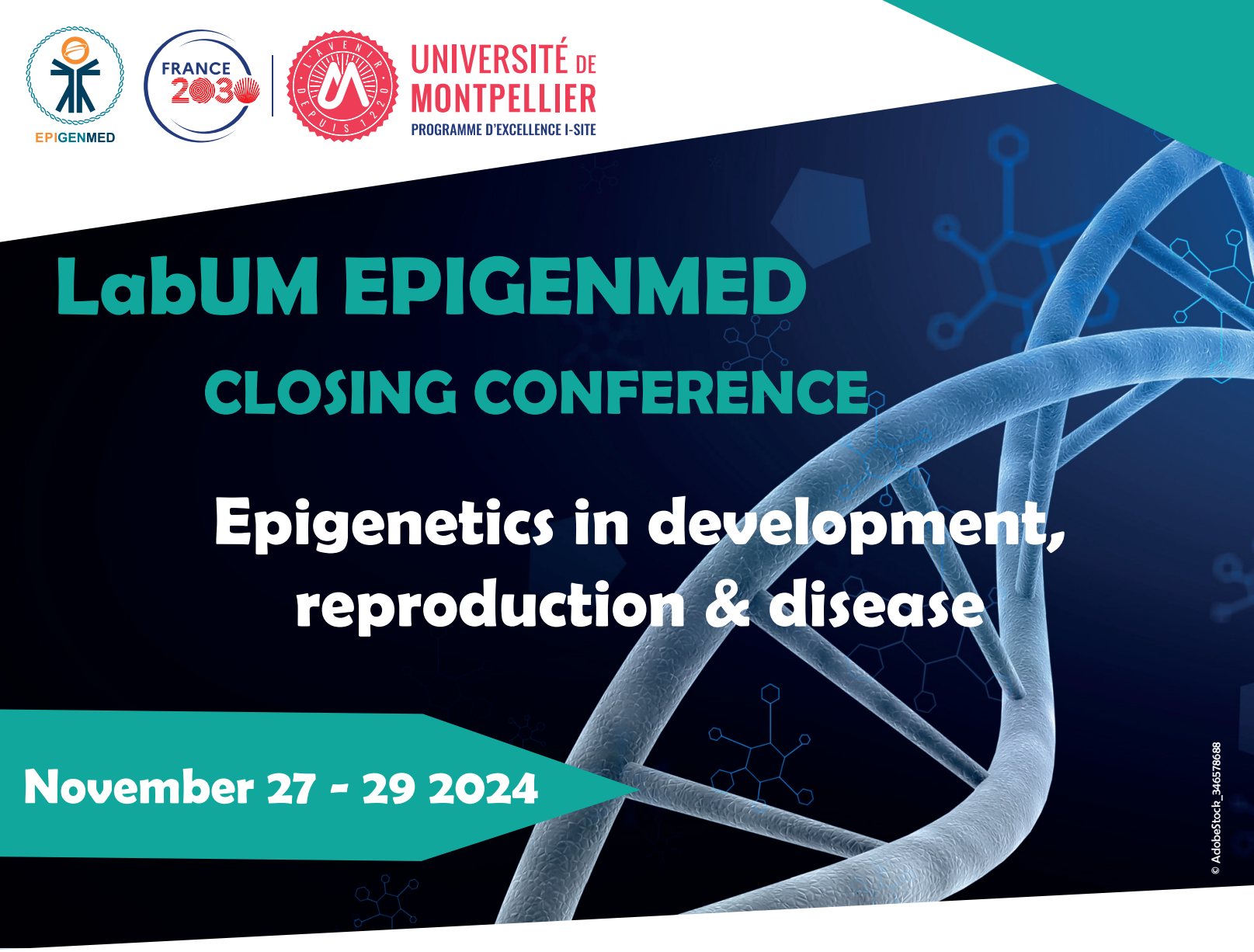
Epigenetics in development, reproduction & disease



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November 27 - 29 2024

- Epigenetic mechanisms in development
- Reproduction and transgenerational inheritance
- Environment, metabolism and epigenetic regulation

ABSTRACT BOOK

Agropolis International
Amphitheatre
1000 avenue Agropolis - Montpellier

PROGRAM

WEDNESDAY NOVEMBER 27

13h00 - 14h00 **Welcome of registered participants**

14h00 - 14h15 **Introduction**

Jacques Mercier - Vice-President in charge of Research University of Montpellier
Robert Feil - Scientific coordinator LabUM EpiGenMed

Session Environment, metabolism and epigenetic regulation
Chair : Rosemary Kiernan, Institute of Human Genetics, FR

14h15 - 15h00 **Paternal exposures and health alter the sperm epigenome and associate with disease in the next generation**
Keynote
Sarah Kimmins, CHUM Univesity of Montréal, CA

15h00 - 15h30 **Epigenetics routes to antifungal drug resistance**
Robin Allshire, University of Edinburgh, UK

Coffee break & poster session

16h15 - 16h45 **When metabolism meets the epitranscriptome: links between pyruvate metabolism and tRNAs acetylation in the Leigh syndrome**
Laurent Le Cam, Institut de Recherche en Cancérologie Montpellier, FR

16h45 - 17h00 **Inherited Health: The Surprising Role of Paternal Diet and Genetic Factors**
Archana Tomar, Helmholtz Munich, DE

17h00 - 17h15 **Microbial Metabolite PreQ1 and its Role in Modulating Host tRNA Modification, Gene Expression, and Cancer Cell Proliferation**
Kuldeep Lahry, Institut de Recherche en Cancérologie Montpellier, FR

17h15 - 17h45 **Discovery of a new regulatory mechanism in the control of histone acetylation**
Carlo Petosa, Institut de Biologie Structurale, FR

17h45 - 18h15 **Chromatin complexes and Metabolic control of self-identity in Drosophila**
Patrick Jouandin, Institut de Recherche en Cancérologie Montpellier, FR

THURSDAY NOVEMBER 28

Session Epigenetic mechanisms in development
Chair: Odil Porrua, Institute of Molecular Genetics of Montpellier, FR

09h00 - 09h45 Keynote
Chromatin remodeling of histone variants underlies the epigenetic inheritance of centromeres
Robert Martienssen, Cold Spring Harbour Laboratory, USA

09h45 - 10h15
X-chromosome reactivation during female mouse development
Maud Borensztein, Institute of Molecular Genetics of Montpellier, FR

10h15 - 10h30
Cracking the (epi)code: Uncovering Rules in Environmental Epigenetic
Patrick Allard, University of California, USA

Coffee break

11h00 - 11h30
Exploring the epigenetic dynamics of imprinted X inactivation during early mouse development
Emma Kneuss, European Molecular Biology Laboratory Heidelberg, DE

11h30 - 12h00
LTRs as drivers of genomic imprinting
Gavin Kelsey, Babraham Institute, UK

12h00 - 12h30
Epigenetic regulation of genome function in development and cancer
Giacomo Cavalli, Institute of Human Genetics, FR

Lunch break & poster session

Session Epigenetic mechanisms in development
Chair: Charlène Boumendil, Institute of Human Genetics, FR

14h00 - 14h30
Uncovering cell fate decisions by integrating transcription factors into RNA-regulatory networks
Julie Carnesecchi, Institute of Molecular Genetics of Montpellier, FR

14h30 - 14h45
Deciphering the chromatin landscape and regulatory logic behind lymphatic endothelial cells using a multi-omic approach
Virginia Panara, Uppsala University, SE

14h45 - 15h15
RNA condensates in oocyte adaptation to quiescence and stress
Arnaud Hubstenberger, Institut de Biologie Valrose, FR

Coffee break

15h45 - 16h15
Germ granule higher-order organization coordinates their different functions
Anne Ramat, Institute of Human Genetics, FR

16h15 - 16h30
Interplay between cell differentiation and chromatin landscape
Lara El Berjawi, IGBMC Illkirch, FR

16h30 - 17h00
Link between pseudouridine, carbohydrate metabolism and drosophila behavior
Jean-Yves Roignant, University of Lausanne, CH

17h00 - 17h30 **The spark of life. Initiating transcription in embryos**
Nadine Vastenhouw, University of Lausanne, CH

Gala Dinner: Brasserie du Corum

FRIDAY NOVEMBER 29

Session Reproduction and transgenerational inheritance
Chair: Martine Simonelig, Institute of Human Genetics, FR

09h00 - 09h45 **Epigenetics, plasticity and evolution in a Lake**
Keynote
Eric Miska, Gurdon Institute, University of Cambridge, UK

09h45 - 10h15 **Meiosis at the heart of epigenetic reprogramming**
Frédéric Berger, Gregor Mendel Institute of Molecular Plant Biology, AT

10h15 - 10h30 **The question of epimutation: How does epigenetic information become heritable?**
Maximilian Fitz-James, University of Oxford, UK

10h30 - 10h45 **Sexually-dimorphic modulation of mammalian embryonic growth by intracellular glycosylation**
Sara Formichetti, European Molecular Biology Laboratory, IT

Coffee break & poster session

11h30 - 12h00 **Small RNAs in Epigenetic Inheritance**
Germano Cecere, Institut Pasteur, FR

12h00 - 12h30 **Paternal effects in mammals: tRNA fragments and beyond**
Ana Boskovic, European Molecular Biology Laboratory Rome, IT

12h30 - 13h00 **Safeguarding germline immortality**
Dónal O'Carroll, University of Edinburgh, UK

13h00 - 13h10 **Closure**

Buffet

Abstracts

Presentations

Paternal exposures and health alter the sperm epigenome and associate with disease in the next generation

Sarah Kimmins[1]

[1]Département de Pathologie et Biologie Cellulaire, Faculté de médecine Université de Montréal – Canada

Abstract

Since the discovery of imprinted genes and their involvement in paternal effects in the next generation, there has been a growing interest in epigenetic programming during spermatogenesis and its connection to offspring health. Complex diseases (e.g. infertility, diabetes, metabolic disorders and cardiovascular disease), and developmental disorders (e.g. neurodevelopmental and birth defects) cannot be attributed to genetics alone. The consequences of paternal environmental exposures on health in the next generation are widely influenced by gene-environment interactions and occur at the level of the sperm epigenome. Over the past decade, epigenomic technologies have made remarkable progress and these advancements have led to the implication of errors in the establishment and maintenance of the epigenome, in embryo development, neurodevelopmental disorders, diabetes and cancer. However, how epigenetic mechanisms drive disease in the next generation remains unresolved. I will present on the state of the field of epigenetic inheritance and explore what is known and how we might address the gaps in knowledge to move beyond association-based studies to truly unravel the underlying mechanisms.

Keywords: Epigenetic inheritance, sperm, epigenome, paternal disease transmission

Epigenetic Routes To Antifungal Resistance

Robin Allshire[1]

[1]Institute for Cell Biology, University of Edinburgh – United Kingdom

Abstract

The assembly of histone H3 lysine 9 methylation (H3K9me)-dependent heterochromatin over genes decreases their transcription. In fission yeast and several pathogenic fungi, heterochromatin is normally concentrated at telomeres and around centromeres. However, changes in the cellular environment can result in the appearance of heterochromatin islands over euchromatic genes1. Such ectopic heterochromatin can be transmitted through cell division, provided the counteracting demethylase, KDM/Epe1, is absent2. Thus, cells may adapt by stochastically forming heterochromatin at various chromosomal locations, with resulting epimutations altering the phenotype of otherwise wild-type cells through reversible gene repression rather than changes in DNA. Previously, we showed that heterochromatin-dependent epimutants, that are resistant to caffeine and widely-used antifungals, form in fission yeast. Isolates with unstable, reversible resistance exhibit distinct heterochromatin islands with reduced expression of underlying genes, including some whose mutation confers resistance. Both caffeine and antifungals down-regulate key counteracting activities (KDM/Epe1 and HAT/Mst2) that normally limit heterochromatin formation, thereby promoting heterochromatin reprogramming1,3. The resulting epimutations allow wild-type cells to cope with unfavourable environments. We are currently investigating what upstream events lead to the formation of such epimutations and the mechanisms underlying their resistance phenotypes. Key questions include: How do epimutants arise? Do they pre-existing in a cell population, or are they induced by external stressors? Do related epigenetic mechanisms contribute to antifungal tolerance/resistance in pathogenic fungi such as Cryptococcus neoformans, that is responsible for _˜200,000 human deaths per annum, or Zymoseptoria tritici, which significantly reduces annual wheat yields globally?

1. Torres-Garcia S, et al. (2020) *Nature* 585:453.

2. Audergon PNCB, et al. (2015) *Science* 348:132.
3. Yaseen I, White SA, et al. (2022) *Nature Structure & Molecular Biology* 29:745.

Keywords: Heterochromatin, mitochondrial dysfunction, pathogenic fungi

Inherited Health: The Surprising Role of Paternal Diet and Genetic Factors

Archana Tomar[1], Melisa Gómez Velázquez[1], Raffaele Gerlini[1], and Raffaele Teperino[1]

[1]Helmholtz Munich – Germany

Abstract

Individual genetics, environmental exposures, and their interactions shape phenotypes, but recent discoveries in epigenetics and Indirect Genetic Effects (IGEs) suggest more complex mechanisms of inheritance. Epigenetic inheritance reveals that acquired traits can be passed across generations, while IGEs highlight that an individual's genotype can influence others' phenotypes intergenerationally.
We examined the intergenerational effects of environmental factors, focusing on paternal exposure to a high-fat diet (HFD) and its impact on offspring health. Short-term paternal HFD exposure induced glucose intolerance and insulin resistance in offspring, traced to alterations in mitochondrial tRNAs (mt-tRNAs) and their fragments (mt-tsRNAs) in sperm. These sncRNAs are transferred to the oocyte at fertilization, affecting early embryonic transcription and adult metabolic phenotypes. Human cohort data further support the association between paternal body mass index (BMI) and offspring metabolic health.

In parallel, we investigates both epigenetic and IGEs in mammalian genetics using data from the International Mouse Phenotyping Consortium (IMPC). We explored whether IGEs are common, their underlying genetic determinants, and their relevance to complex diseases. Our findings reveal that IGEs are widespread in mammalian genetics and influence metabolic, neurological, and cardiovascular traits. Genetic factors driving IGEs are strongly associated with proteins involved in protein ubiquitination and neuroactive signaling.
Together, these findings emphasize the complex interplay of genetic and environmental factors in shaping intergenerational inheritance. IGEs and (epi)genetic mechanisms, such as sperm-borne mt-tRNAs, act in gene-dependent but genotype-independent ways, regulating physiology and disease susceptibility across generations. This expands our understanding of inheritance and opens new avenues for exploring the genetic basis of complex traits and diseases in humans.

Keywords: Epigenetic inheritance, Indirect Genetic Effects (IGEs), High, fat diet (HFD), Mitochondrial tRNAs (mt, tRNAs), Intergenerational inheritance

Microbial Metabolite PreQ1 and its Role in Modulating Host tRNA Modification, Gene Expression, and Cancer Cell Proliferation

Kuldeep Lahry[1], Wen Zhang[2], Denis Cipurko[3], Sihao Huang[2], Olivia Zhibley[2], Luke R. Frietz[2], Mahdi Assari[2], Christopher D. Katanski[2], Marisha Singh[2], Aurore Attina[4], Hélène Guillorit[1], Christopher P. Watkins[2], Delphine Gourlain[5], Didier Varlet[5], Hankui Chen[2], Françoise Macari[1], Kate Johnson[3], Nicolas Chevrier[3], Tao Pan[2], and Alexandre David[1,4]

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Abstract

The microbiome interacts with its eukaryotic host through various metabolites, influenc-ing cell physiology. One specific molecular pathway of this interaction involves the modi-fication of host tRNA with queuosine (Q), a process that utilizes the microbial metabolite queuine. While microbes produce the precursor metabolite pre-queuosine1 (preQ1) in their own queuosine biosynthesis pathway, its effects on host cell biology and the underlying mech-anisms have not been explored.

Our research shows that preQ1 significantly inhibits the proliferation of human and mouse cells; however, this inhibitory effect is suppressed or reversed when queuine is present, as queuine competes with preQ1 for tRNA modification. We have demonstrated that when preQ1 is incorporated into tRNA, it disrupts protein synthesis, markedly alters gene ex-pression, and inhibits the proliferation of cancer cell lines in both humans and mice, while non-cancerous fibroblast cells remain unaffected. Mechanistically, preQ1 selectively reduces cognate tRNA levels and impairs the translation of housekeeping genes in a codon-dependentmanner. We identified that the inositol-requiring enzyme 1 (IRE1) ribonuclease is responsi-ble for the selective degradation of preQ1-modified tRNAs on translating ribosomes.

Additionally, preQ1, like queuine, is naturally present in the plasma and tissues of mice. In our studies, preQ1 treatment reduced tumour growth in a xenografted cancer mouse model without affecting healthy tissues. However, its efficacy is limited by competition with queuine for tRNA incorporation via the TGT enzyme and by a "bell-shaped" dose-response curve at higher concentrations.

To overcome these limitations, we developed a series of synthetic queuine analogues and identified one, analogue 5, that exhibits a similar inhibitory effect on cancer cell lines but with a more favourable, linearly increasing competitive efficiency. Overall, our research highlights the role of the microbiome in regulating host gene expression and presents natural metabolites from the microbiota as a potential source of novel anti-cancer therapeutics.

Keywords: Microbiome, Microbial metabolites, PreQ1, tRNA modification, Cancer therapeutics

Discovery of a new regulatory mechanism in the control of histone acetylation

Domenico Iuso[1]†, Isabel Garcia-Saez[2], Yohann Couté[3], Yoshiki Yamaryo-Botté[1], Elisabetta Boeri Erba[2], Annie Adrait[3], Nour Zeaiter[4], Malgorzata Tokarska-Schlattner[4], Zuzana Macek Jilkova[1,5], Fayçal Boussouar[1], Sophie Barral[1], Luca Signor[2], Karine Couturier[4], Azadeh Hajmirza[1], Florent Chuffart[1], Ekaterina Bourova-Flin[1], Anne-Laure Vitte[1], Lisa Bargier[6], Denis Puthier[6], Thomas Decaens[1,5], Sophie Rousseaux[1], Cyrille Botté[1], Uwe Schlattner[7], Carlo Petosa[2*], Saadi Khochbin[1*]

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7 Université Grenoble-Alpes, INSERM, Institut Universitaire de France, Laboratory of Fundamental and Applied Bioenergetics, Grenoble, France.
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Abstract

The synthesis of fatty acids from acetyl-CoA is deregulated in diverse pathologies, including cancer. We have identified Nucleoside Diphosphate Kinases 1 and 2 (collectively named NME1/2) as negative regulators of fatty acid accumulation. NME1/2 are housekeeping enzymes involved in nucleotide homeostasis that were recently discovered to bind Co-enzyme A (CoA). We show that NME1 also binds acetyl-CoA and that ligand recognition involves a unique binding mode dependent on the CoA/acetyl-CoA 3' phosphate. We report that Nme2 knockout mice fed a high-fat diet (HFD) exhibit excessive triglyceride synthesis and liver steatosis. In liver cells NME2 mediates a gene transcriptional response to HFD leading to the repression of fatty acid accumulation and activation of a protective gene expression program via targeted histone acetylation. Our findings implicate NME1/2 in the epigenetic regulation of a protective liver response to HFD and suggest a potential role in controlling acetyl-CoA usage between the competing paths of histone acetylation and fatty acid synthesis.

Keywords: Fatty acid synthesis, histone acetylation, acetyl-CoA, Nucleoside Diphosphate Kinase

Chromatin complexes and Metabolic control of self-identity in Drosophila

Patrick Jouandin[1]

[1]Institut de Recherche en Cancérologie de Montpellier – IRCM, Institut de Recherche en Cancérologie de Montpellier, INSERM U1194, Université de Montpellier, Institut régional du Cancer de Montpellier, Montpellier, F-34298, France – France

Abstract

To eliminate unfit cells within host's tissues, the immune system must discriminate between healthy and damaged cells. Deregulation of this process leads to autoimmune and inflammatory disorders, as well as impaired antitumor immunity. However, the mechanisms at play are poorly understood, which limits our ability to develop new therapies. In particular, the signals expressed by the tissues to communicate their physiological status to the immune cells and trigger the appropriate response remain understudied. This is largely due to the lack of genetic models amenable to systematically investigate the communication between host's tissues and the immune cells. To address this issue, we use the genetically tractable *Drosophila* to study the interaction between the adipose tissue and the immune cells *in vivo*. Specifically, we interrogate the epigenetic and metabolic programs implicated in inflammation and self-tolerance, which processes are deregulated in most cancers. Through medium throughput genetic screen *in vivo*, we identified key conserved components of the epigenetic and metabolic machinery, which downregulation in the adipose tissue triggers an inflammation, and in extreme cases an autoimmune response. These include most members of the NuRD, Tip60 and SWI/SNF chromatin remodeling complexes, as well as several metabolic enzymes encompassing nine metabolic pathways, which altogether appear to regulate N-glycosylation, a process involved in the secretion machinery that has been linked to self-tolerance by the immune cells. We propose that self-tissues convert their physiological status into metabolic cues, which in turn impact on the secretion of signals that dictate the appropriate immune response. We are currently characterizing this model at the molecular level with emphasis on the chromatin-metabolism network.

Keywords: Metabolism, chromatin, Immunity, drosophila

X-chromosome reactivation during female mouse development

Maud Borensztein[1]

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Abstract

In mammals, the formation of the primordial germ cells (PGCs), precursors of the gametes, leads to the repression of the somatic programme and the expression of germline-specific genes, accompanied by a extensive epigenetic remodelling. This reprogramming includes genome-wide DNA demethylation, significant redistribution of histone marks, erasure of genomic imprints, and, in females, the reactivation of the inactive X chromosome (Xi).
Xi reactivation occurs first through the loss of *Xist* long non-coding RNA coating, followed by the erasure of repressive chromatin marks and the biallelic expression of X-linked genes. Despite this knowledge, little is known about the dynamics of X-linked gene reactivation and the mechanisms involved during Xi reactivation in the germline. To explore the chromosome-wide kinetics of Xi reactivation, we have used *in vivo* single-cell allele-specific RNAseq, complemented by low input CUT&RUN for histone marks during female PGC development. We show that X-linked genes are sequentially activated as previously described for the inner cell mass of the blastocyst and iPSCs, but with different dynamics and requirements. In PGCs, we observed a reactivation dependency on *Xist* RNA loss, repressive chromatin marks, and genomic location.
We are now conducting further studies to better understand the mechanisms underlying Xi reprogramming in the context of female development, which include the development of *in vitro* gametogenesis and CRISPR KO screens to study Xi reactivation. Together, these investigations open up the way for a better understanding of the requirements for epigenetic reprogramming in females.

Keywords: X chromosome, embryo, germline, transcription

Cracking the (epi)code: Uncovering Rules in Environmental Epigenetics

Patrick Allard[1]

[1]University of California [Los Angeles] – United States

Abstract

The overarching goal of our research is to understand how environmental cues trigger a deregulation of the epigenome that can resist epigenetic reprogramming in germ cells and therefore can become heritable. We will focus our presentation mainly on the model epigenetic toxicant inorganic arsenic (iAs). Inorganic arsenic (iAs) is a model epigenetic toxicant owing to its impact on global DNA hypomethylation coinciding with a reduction in the levels of the universal methyl donor SAM, used towards DNA and histone methylation. iAs is also a chemical with well-established transgenerational epigenetic inheritance effects, producing heritable reproductive and metabolic dysfunctions and neurobehavioral outcomes for multiple generations. However, iAs shows remarkable complexity in its epigenetic impact since even in the context of global DNA hypomethylation, some loci show hypermethylation and the effect on histone methylation are non-uniform with many methylated histone marks showing increases while others show a decrease. It is unclear how iAs causes such varied epigenetic effects and how these effects are maintained during developmental reprogramming. Here, we will present our most recent data linking the expression, location, and activity of two enzymes crucial for the one-carbon and iAs metabolism, MAT2A and AS3MT, respectively, and their role in guiding the locus-specific epigenetic response to arsenic in mouse embryonic stem cells.

Keywords: Environment, Epigenetics, Arsenic, histone PTMs

Exploring the epigenetic dynamics of imprinted X inactivation during early mouse development.

Emma Kneuss[1] and Edith Heard[1,2]

[1]European Molecular Biology Laboratory – Germany
[2]Collège de France – Chaire Epigénétique et mémoire cellulaire – France

Abstract

The process of X-chromosome inactivation (XCI), which involves the developmental silencing of most genes on one of the two X chromosomes in female mammals, ensures dosage compensation between the sexes in response to the genetic imbalance between XX females and XY males. XCI is a tightly regulated process that occurs during early embryogenesis, and its initiation and establishment were long thought to be restricted to these stages.
The initiation of XCI depends on the expression of the long non-coding RNA Xist, which is transcribed from and coats the future inactive X chromosome. Studies in mouse embryonic stem cells have shown that Xist RNA recruits the transcriptional repressor SPEN to the X chromosome. SPEN subsequently integrates multiple epigenetic and trans-acting factors including chromosome remodelling complexes, associated histone deacetylases, RNA processing complexes, the m6A RNA methylation machinery, which are thought to be essential for XCI. How these mechanisms functionally regulate XCI and the kinetics of silencing across distinct X-linked genes remain open questions, as do the relative contributions of each SPEN interactor. Moreover, an understanding of the roles of these factors *in vivo* is lacking. Our ongoing work will be described, elucidating the role of SPEN in XCI *in vivo*, as well as the specific contributions of the different protein complexes recruited by SPEN to the XCI process during preimplantation development. Furthermore, our recent studies demonstrating the role of Xist RNA and SPEN in ensuring XCI well beyond early embryogenesis, will also be presented.

Keywords: X chromosome inactivation, Transcriptional gene silencing, early mouse development

LTRs as drivers of genomic imprinting

Gavin Kelsey[1,2,3], Christian Belton[1,2], Carmen Jones[1], Teruhito Ishihara[1], and Asif Nakhuda[1]

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[3]Wellcome-MRC Institute of Metabolic Science-Metabolic Research Laboratories, Cambridge – United Kingdom

Abstract

Development of the mammalian germline is characterised by the establishment of highly specialised epigenomes in the egg and sperm. Much of the gametic DNA methylation and chromatin profiles are reprogrammed at the onset of embryonic development, and this may be necessary for orderly activation of the embryonic genome. Some gamete-derived epigenetic states survive embryonic reprogramming, for example, in the case of imprinting. The principles, DNA mediators and functional significance of 'classical' imprinting determined by gametic DNA methylation marks are well established. Imprinting can also be conferred by gametic chromatin states, and this more recently discovered mode of imprinting has been coined 'non-canonical imprinting'. We have identified long terminal repeats (LTRs) of endogenous retroviral insertions as potential mediators of non-canonical imprinting. These LTRs have been co-opted as alternative tissue-specific promoters or enhancers, characterised by monoallelic activity specifically in placental lineages. We are exploring the functional impact of LTR-based imprinting using specific knock-outs in stem cells and *in vivo*, as well as seeking to understand how these LTRs are epigenetically regulated from the egg to the embryo.

Keywords: imprinting, LTRs, germline, placenta

Epigenetic regulation of genome function in cell physiology and cancer

Giacomo Cavalli[1,2]

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[2]Institut de Génétique Humaine – CNRS, CNRS : UMR9002, CNRS : UPR1142 – France

Abstract

Epigenetic components regulate many biological phenomena during development and normal physiology. When dysregulated, epigenetic components can also accompany or drive diseases. One main class of epigenetic components are Polycomb group proteins. Originally, Polycomb proteins were shown to silence gene expression. In the *Drosophila* system, we found that this function involves the regulation of 3D chromosome folding and we found that Polycomb components can induce the formation of long-distance interactions or chromatin loops that may play instructive roles in gene regulation. Furthermore, perturbation of Polycomb components leads to tumorigenesis in flies. S urprisingly, e ven u pon a transient depletion followed by restoration of the full Polycomb compendium, epithelial cells lose their normal differentiated f a te a n d c ontinue p r oliferating, d emonstrating t h at m a lignant tumors can have an epigenetic origin. Inspired by these results in flies, w e t e sted w h ether epigenetic memory can also apply to mouse ES cells and perturbed chromatin organization by a transient inhibition of histone deacetylases. We found that acute inhibition induces gene expression, chromatin composition and 3D genome folding changes. Strikingly, some of the 3D genome changes can not be reverted upon restoration of the initial histone acetylation conditions. Upon a second pulse of inhibitor treatment, hundreds of genes can no longer restore their initial expression state, suggesting that cells can record a previous perturbation and maintain an altered functional state.

Acknowledgements
This work was supported by the European Research Council Advanced Investigator grant (3DEpi), by the "Fondation ARC pour la recherche sur le cancer", by the "Fondation pour la recherche médicale" (FRM), by INSERM and the ITMO Cancer (MMTT project), by the INCa, the E-RARE IMPACT grant under the ERA-NET Cofund Horizon 2020 scheme, by the MSD-Avenir foundation and by the CNRS.

Keywords: Polycomb, cancer, 3D genome, drosophila, ES cells

Uncovering cell fate decisions by integrating transcription factors into RNA-regulatory networks

Constanza Blanco[1], Wan Xiang[1,2], Panagiotis Boumpas[1,3], Maily Scorcelletti[1,3], Samir Merabet[4], and Julie Carnesecchi[5]

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[5]Institut de Génétique Moléculaire de Montpellier – CNRS – France

Abstract

Transcription factors (TFs) are key players in gene expression, acting on DNA regulatory sequences to coordinate morphogenetic programs. Beyond this DNA-centric viewpoint, several TFs interact with RNA and regulate alternative splicing, thus diversifying their gene-regulatory repertoire. Yet, the mechanisms by which TFs influence splicing and how TF-RNA function contributes to tissue morphogenesis remain elusive. We address this issue for the Drosophila Hox protein Ultrabithorax (Ubx), a central TF in metazoan development. By examining physical and functional interactions between wild-type and DNA-binding mutant proteins, we uncover a homodimerization mechanism employed by Ubx to regulate splicing, which relies on its ability to bind DNA and RNA. Moreover, we identify a key residue in the Ubx homeodomain critical for its RNA-binding ability and splicing activity. Overall, our work reveals that Ubx-RNA binding activity is integral to its function in morphogenesis through interaction with splicing factors for muscle formation and contributing to the fundamental Hox homeotic functions in cell identity. We thus propose a refined model for the Ubx splicing function wherein TF-DNA/RNA binding and dimerization are essential for connecting transcription and splicing spatially. Our research highlights the critical integrative function of TF-DNA and TF-RNA binding in orchestrating morphogenetic programs during animal development.

Keywords: Gene regulation, Transcription Factor, Hox, Splicing, DNA, RNA, development, Drosophila

Deciphering the chromatin landscape and regulatory logic behind lymphatic endothelial cells using a multi-omic approach

Virginia Panara[1,2,3], Hannah Arnold[1], Marleen Gloger[1], Anna Johansson[4], Renae Skoczylas[1], Agata Smialowska[4], and Kaska Koltowska[1,5]

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[3]Institut des Sciences de l'Evolution de Montpellier – Université Montpellier I – France

[4]Department of Cell and Molecular Biology, National Bioinformatics Infrastructure Sweden, Science for Life Laboratory, Uppsala University – Sweden

[5]Beijer Gene and Neuro Laboratory, Uppsala University – Sweden

Abstract

Switching genes on and off is a fundamental part of development, ensuring that a unique molecular code is set up to orchestrate tissue morphogenesis. Changes in chromatin organisation dictate accessibility to gene regulatory elements and control gene expression. During embryonic development, zebrafish lymphatic endothelial cells differentiate from the venous endothelium. Several molecular factors regulating lymphatic endothelial cells (LECs) specification and differentiation have been identified. However, how the chromatin organisation differs between lymphatic and blood endothelium and how these differences are reflected in gene expression remains to be determined.

In this study, we combined ATAC-seq and Hi-C to characterise the accessibility and 3D architecture of chromatin in LECs and BECs. We uncovered cell-type specific chromatin organisation at a global level, revealing differential preference for promoter interactions between LECs and BECs. Combining chromatin characterisation with single cell RNA-seq, we investigated the regulatory logic for nine genes whose expression is enriched in LECs. We used a transgenesis approach to validate the candidates and confirmed that short- and long-range enhancers of *tbx1* and *mafba* can drive expression in LECs, highlighting the potential of our combinatorial approach. We then focused on the known lymphatic factor *mafba* and reconstructed its tissue-specific regulatory networks by identifying its downstream targets using TF footprinting.

Overall, our work has produced powerful multi-omic datasets that can be used to systematically determine the regulatory networks governing LEC identity.

Keywords: vasculature, HiC, ATAC, seq, enhancers, lymphatics, zebrafish

Germ granule higher-order organization coordinates their different functions

Anne Ramat[1], Ali Haidar[1], Céline Garret[1], and Martine Simonelig[1]

[1]Institut of Human Genetics – CNRS – France

Abstract

Most RNA-protein (RNP) condensates are composed of heterogeneous immiscible phases. However, how this multiphase organization contributes to their biological functions remains largely unexplored. *Drosophila* germ granules, a model of RNP condensates, are the site of mRNA storage and translational regulations. Here, using super-resolution microscopy and single-molecule imaging approaches, we show that germ granules have a biphasic organization and that translation occurs in the outer phase and at the surface of the granules. Using single-molecule FISH (smFISH), we showed that the localization, directionality, and compaction of mRNAs within the granule depend on their translation status, with translated mRNAs being enriched in the outer phase with their 5end oriented towards the surface. Translation is strongly reduced when germ granule biphasic organization is lost. This work reveals the intimate links between the architecture of RNP condensates and the organization of their different functions, highlighting the functional compartmentalization of these condensates.

Keywords: RNP condensate, mRNA translation, development, Drosophila

Interplay between cell differentiation and chromatin landscape

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Abstract

Stem cells exhibit the ability to differentiate into different cell types, a process governed by a complex interplay of regulatory factors, including transcription factors and epigenetic mechanisms. Existing studies tend to emphasize the significance of each regulatory level individually, overlooking their collaborative function.
The Glial cells missing/Glial Cell deficient (Gcm) transcription factor (TF), identified by our lab as the master regulator during *Drosophila* gliogenesis, acts as a switch between glial and neuronal fates and is necessary and sufficient to induce glial differentiation. Such a strong potential indicates that Gcm is sufficient to recruit factors necessary for shaping the chromatin into a specific identity, providing a unique asset to study stem cell differentiation *in vivo*.

In this study, we investigate the coordinated action of the TF Gcm, alongside chromatin remodelers and chromatin-modifying enzymes, in directing the differentiation of *Drosophila* neural stem cells, neuroblasts, into glial cells.

Our findings in *Drosophila* S2 cells, reveal that Gcm expression induces significant alterations in chromatin conformation, transitioning genes typically in a heterochromatic state to an active chromatin configuration. These data suggest that Gcm may act as a pioneer TF because it may have nucleosome binding properties. Indeed, we show by Electrophoretic mobility shift assays (EMSA) that Gcm can bind chromatin wrapped around nucleosomes, demonstrating its role as a pioneer TF.
Ongoing *in vivo* experiments, including immunoprecipitation followed by mass spectrometry, aim to elucidate the interactions between Gcm and epigenetic modifications in regulating stem cell differentiation, shedding light on the collaborative dynamics that drive this process.

Keywords: stem cell, cell differentiation, transcription factor, chromatin

Pseudouridine synthase 7 controls aggressiveness through modulation of glycolysis

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Abstract

Pseudouridine (Ψ) is the most abundant RNA modification found in all types of RNA. It is deposited by Ψ synthases (Pus) and is required to stabilize the RNA structure. Patients carrying alteration in the *Pus7* gene suffer from developmental delay, intellectual disability, microcephaly, hyperactivity and increased aggression levels. Here we show that the *Pus7* mutation in human patient cells and in a drosophila model lead to the loss of Ψ at position 13 in several tRNA, which is associated with a specific decrease of tRNA:Aspartate (tRNAAsp) level. Consistently, ribosome profiling shows slow decoding specifically at Aspartate codons that triggers the integrated stress response (ISR). This ultimately leads to a metabolic shift towards increased glycolysis and reduced mitochondrial respiration. Overexpressing tRNAAsp, inhibiting the ISR or dampening the glycolytic pathway is sufficient to rescue the aggressiveness phenotype, demonstrating the involvement of the tRNAAsp-ISR-glycolysis axis in this behavior. Together our data provide new insights into the molecular defects associated with the loss of Pus7 and suggest potential new avenues for therapeutic treatment.

Keywords: Pus7, tRNA, RNA modifications, glycolysis

The spark of life. Initiating transcription in embryos.

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Abstract

The localization of transcriptional machinery in specialized transcription bodies is a hall-mark of gene expression in eukaryotic cells. In spite of the attention these bodies have received in recent years, it is not so clear how they form, and if and how they affect gene expression. It is generally difficult to address these questions because bodies are often small, short-lived, and highly abundant. Furthermore, without knowing the sequence that nucleates their formation, it is impossible to perturb them specifically. We have taken advantage of two prominent transcription bodies that mark the onset of transcription during zebrafish embryogenesis to address some of these questions. Here, I will talk about our latest results regarding the formation and function of transcription bodies.

Keywords: zebrafish, transcription, condensates, chromatin

Meiosis at the heart of epigenetic reprogramming

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Abstract

In mammals, genomic imprinting results from different sets of epigenetic marks that distinguish the parental origins of loci in the progeny. Epigenetic reprogramming of genomic imprinting is necessary to establish a totipotent cell state. The consecutive erasure of parental epigenetic marks and the deposition of new marks occurs alongside major life stage transitions including gametogenesis and fertilization. However, despite occurring concomitantly with gametogenesis, the role of meiosis in epigenetic reprogramming has received little attention. To address this question, we use the model bryophyte *Marchantia polymorpha*. Following the haploid reproductive phase of this land plant, the expression of the paternal genome is silenced by the histone modification H3K27me3 in the short-lived diploid embryo. We show that imprinting is erased during meiosis, which occurs separately from gametogenesis and fertilization in Marchantia. The epigenetic reprogramming initiated during meiosis is completed in the meiotic spores where the chromatin landscape of the next haploid generation is established *de novo*. Hence, our findings illustrate a potential role for meiosis in epigenetic reprogramming that may be generalized to other sexually reproducing species.

Keywords: meiosis, imprinting, reprogramming

The question of epimutation: How does epigenetic information become heritable?

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Abstract

As well as specifying differences between cell types within an individual, epigenetic information is also a major source of variation between individuals within a population. While this epigenetic variation is often restricted to a single generation, it can in some cases become heritable by "epimutation". Epimutation may occur spontaneously, or be induced by a specific event, such as an environmental trigger, but the mechanisms and prevalence of these processes are not clear.

In one example of epimutation in Drosophila, a transient genetic change at one locus, a deletion lasting only a single generation, leads to epimutation of another distant locus resulting in heritable differences in histone modifications, with effects on gene expression and phenotype, that persist for many generations. We showed that this transient deletion leads to an increase in chromatin contacts between the two distant loci, implicating 3D chromatin organisation in epigenetic inheritance. We artificially recapitulate these chromatin contacts using a synthetic biology system that is able to trigger epigenetic inheritance without any genetic change, providing a mechanism for this case of epimutation through trans effects.

Another question is how much these and other mechanisms of epimutation contribute to heritable variation in natural populations. To investigate this, we will follow different populations of Drosophila over several generations under different conditions. By profiling their histone modifications and gene expression in each generation, we will be able to map the appearance of new epimutations and track them across generations. This will provide an unbiased reading of the epimutation rate under both natural conditions (i.e. "spontaneous" epimutations) and in response to potential environmental triggers (i.e. "induced" epimutations) to determine the broader contribution of epigenetic information to heritable phenotypes.

Keywords: Epimutation, Epigenetic Inheritance, Chromatin Organisation, Drosophila, Polycomb, Histone Modifications

Sexually-dimorphic modulation of mammalian embryonic growth by intracellular glycosylation

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Abstract

The main form of intracellular glycosylation in animals is **O-GlcNAcylation**, the reversible linkage of a monosaccharide (O-GlcNAc) to serine and threonine protein residues. The donor substrate for O-GlcNAc, UDP-GlcNAc, is the end product of a metabolic pathway **responsive to nutrient levels**. O-GlcNAc is present on thousands of mammalian proteins in all cellular compartments, especially in the nucleus and **including RNA Polymerase II and transcription factors OCT4 and SOX2**. An ever-increasing number of in vitro studies report the regulation by O-GlcNAc of essential cellular functions such as cell cycle, translation, glycolysis, transcription. In spite of its pleiotropy, only one enzyme is responsible for O-GlcNAcylation, called O-GlcNAc transferase (OGT). The mammalian *Ogt* gene is essential for both cellular proliferation and embryonic development. Specifically, **a functional maternal *Ogt* copy is required for the mouse embryo to pass the blastocyst stage**. Because of this obstacle for genetics studies, the molecular function of O-GlcNAc in early mammalian development remains poorly understood and certainly never addressed in vivo. We addressed O-GlcNAc's role in the early mouse embryo through two parallel routes both overcoming cellular and embryonic lethality: i. We **depleted the O-GlcNAc modification itself from the embryonic nuclei,** by overexpressing in the zygote the enzyme catalyzing O-GlcNAc removal; ii. We created four *Ogt*-hypomorphic mouse models with OGT's catalytic activity reduced to a range of degrees. By analyzing the transcriptome of single embryos at key pre- and postimplantation stages upon different level of disruption of O-GlcNAc homeostasis, we discovered that nuclear O-GlcNAc is dispensable for embryonic genome activation and blastocyst differentiation, but that **reducing O-GlcNAc slows down embryonic growth**. Due to the location of *Ogt* on the X chromosome, **male embryos are more susceptible to *Ogt* disruption**. Our studies established a novel link between a maternally-transmitted intracellular protein glycosylation and developmental pace, with sexually-dimorphic penetrance.

Keywords: glycosylation, OGlcNAc, OGT, mouse preimplantation embryo, embryonic development, embryonic genome activation, single embryo transcriptomics

Small RNAs in Epigenetic Inheritance: a lesson from worms

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Abstract

Heritable traits have traditionally been attributed to mutations in germline DNA. However, emerging research reveals the pivotal role of epigenetic mechanisms, including DNA methylation, histone modifications, and small RNAs in transmitting non-genetic information across generations. In our laboratory, we explore the role of small RNAs in epigenetic inheritance using the model organism *Caenorhabditis elegans*. In my talk, I will present our findings, emphasizing the remarkable ability of small RNAs to transmit traits across generations. I provide a case study of small RNAs that progressively reduce fertility in subsequent worm generations and delve into the underlying molecular mechanisms facilitating their transgenerational transmission. Moreover, I will present recent results on the intriguing phenomenon of small RNAs migrating from the soma to the germline, enabling the inheritance of environmentally acquired information and stress resilience.

Keywords: Epigenetics, intergenerational inheritance, small RNAs, miRNAs, piRNAs, stress resilience, environmentally acquired traits

Paternal effects in mammals: tRNA fragments and beyond

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Abstract

Phenotypic diversity within and between species cannot be fully explained by differences in the primary DNA sequence. Indeed, the interpretation of genetic information (i.e. gene expression) is finely modulated by interactions of genetic and epigenetic factors.
Thanks to their dynamic nature, epigenetic marks represent the ideal molecular tool at disposition of living organism to rapidly wire their genetic output in response to environmental perturbations, without permanent changes of the genome. Furthermore, epialleles carried in the gametes that survive the near-global epigenetic reprogramming taking place after fertilization, have the potential to regulate gene expression of embryos, eventually resulting in phenotypic shifts in adult organisms.
Diet has a crucial role on human health and disease propensity, with broader consequences on multiple aspects of society. Alongside, unhealthy dietary habits during or before conception represents a risk factor for offspring metabolic disorder across different species.
We use a murine inheritance paradigm induced by paternal low protein diet (LPD), previously reported to affect offspring liver cholesterol metabolism, potentially through sperm-borne small RNAs, to ask:
i) what is the scope of paternal contribution to phenotypic traits triggered by nutritional interventions,

ii) can small RNAs serve as bona vide carriers of epigenetic information between generations in mammals, and

iii) what are the molecular events during early development that bridge the paternal LPD consumption with measured F1 phenotypes?
Our work will contribute to the understanding of the molecular mechanisms that govern the relationship between paternal nutrition and the developmental origins of metabolic syndromes, with important consequences for public health and disease risk in humans.

Keywords: Diet, Epigenetics, small RNAs, Inheritance

Abstracts

Posters

Dynamics of RNF113A methylation and its role in SCLC sensitivity to alkylation damage

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Abstract

Small cell lung cancer (SCLC) represents the most lethal form of lung cancer, with poor survival due in part to chemoresistance towards limited available therapeutic agents. We have previously established that lysine methyltransferase SMYD3-mediated methylation of RNF113A obstructs its interaction with the phosphatase PP4 and sustains its phosphorylation levels and E3 ligase activity. This active form of RNF113A leads to better activation of the ASCC damage repair pathway and promotes cellular resistance to alkylation damage. Remarkably, SMYD3 inhibition revives the sensitivity of SCLC cells to alkylating drugs and improved response to chemotherapy.

Here, we aimed to demonstrate the potential dynamics of this methylation event. Using in vitro demethylation assays and mass spectrometry, we identified a SMYD3-counteracting demethylase, which showed specific activity against methylated RNF113A dimethylated peptides. Besides in vitro characterization of its activity, we confirmed that this demethylase down-regulates SMYD3-mediated RNF113A methylation in cells. We report one of the very first example of specific non-histone demethylation activity by a demethylase, illustrating the dynamic regulation of RNF113A methylation with potential consequences on SCLC sensitivity to chemotherapy. Indeed, bioinformatics analysis suggests that this demethylase might be enriched in a specific SCLC subtype, suggesting that some tumors might be more sensitive to alkylating therapy than others. We are now assessing the consequences of RNF methylation dynamics on SCLC cell tolerance to alkylation-based DNA damage. A better understanding of the effectors at play will ultimately help to optimize the therapeutic repertoire against this deadly lung cancer.

Keywords: Protein Methylation/Demethylation, Small Cell Lung Cancer, Chemoresistance, Epige-netics

Sperm derived H2AK119ub1 is required for embryonic development in Xenopus Laevis

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Abstract

Deposition of H2AK119ub1 by the polycomb repressive complexe-1 plays a key role in the initiation of facultative heterochromatin formation in somatic cells. Here we evaluate the contribution of sperm derived H2AK119ub1 to embryo development. In Xenopus laevis we found that H2AK119ub1 is present during spermiogenesis and into early embryonic development, highlighting its credential for a role in the transmission of epigenetic information from the sperm to the embryo. In vitro treatment of sperm with USP21, a H2AK119ub1 deubiquitylase, just prior to injection to egg, results in developmental defects associated with gene upregulation. Sperm H2AK119ub1 editing disrupts egg factor mediated paternal chromatin remodelling processes. It leads to post-replication accumulation of H2AK119ub1 on repeat element of the genome instead of CpG islands. This shift in post-replication H2AK119ub1 distribution triggered by sperm epigenome editing entails a loss of H2AK119ub1 from genes misregulated in embryos derived from USP21 treated sperm. We conclude that sperm derived H2AK119ub1 instructs egg factor mediated epigenetic remodelling of paternal chromatin and is required for embryonic development. A key process in the transmission of paternal epigenetic cues to the embryos is their interaction with maternal components. In the next step, we will deploy complementary proteomic approaches to single out egg factors that interact with the epigenetically programmed fraction of sperm chromatin.

Keywords: sperm, epigenetic, transmission, histone modification

Modeling RNA structure in biomolecular condensed phases by atomistic simulations

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Abstract

Biomolecular condensates formed through liquid-liquid phase separation (LLPS) of proteins and RNAs are nowadays accepted to play a key role in cellular organisation. Despite the ever-growing attention for these membraneless organelles, a microscopic picture of the internal organization of condensates is still missing and their dynamical and structural properties at the molecular scale are still elusive, even for model in vitro systems.
Recently, our group has introduced a fragment-based strategy to investigate the microscopic origin of LLPS by accurate explicit-solvent all-atom MD simulations. This approach is based on the MD simulation of high-concentration mixtures of small-sized peptides and/or oligonucleotides, to probe intermolecular interactions in conditions that mimic real condensates while keeping, at the same time, the computational cost reasonable (1,2).

Building on these findings, we extended this approach to structured RNA fragments in order to shed light on their conformational ensemble in biomolecular condensates and in particular, we focused on a previously well-characterized GCAA tetraloop (3). We mimicked the physico-chemical environment within a biomolecular condensate by simulating the tetraloop in a arg-rich peptide solution with a concentration comparable to those measured in model in vitro condensates.

We observed that our model condensate significantly influenced the conformational dynamics of RNA tetraloop, favoring the unfolding process and strongly stabilizing extended conformations of RNA.

(1) Paloni et al., J. Phys. Chem. B 2020, 124, 9009 - 9016

(2) Paloni et al., Protein Science. 2021, 30, 1418 - 1426
(3) Zerze et al., J. Phys. Chem. B 2021, 125, 50, 13685 - 13695

Keywords: Biomolecular condensate rna dynamics

The imprinted lncRNA Meg3 in DNA damage-induced stress responses in neurons

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Abstract

Meg3 is an imprinted, nuclear, lncRNA produced from the maternal chromosome in a large ncRNA polycistron at the *Dlk1-Dio3* domain. This locus has roles in development and disease and regulates neurodevelopment. Our lab showed that Meg3 lncRNA prevents in *cis* the upregulation of *Dlk1*, which encodes an antagonist of Notch (Sanli I. *et al.*, Cell Reports, 2018; Farhadova S. *et al.*, Nucleic Acids Research, 2024). However, little is known about the putative *trans* roles of this conserved lncRNA.

We find that upon differentiation of murine embryonic stem cells (mESCs) to neural cells, Meg3 changes its localization from a single *cis* focus to multiple *trans* foci. Using magnet-activated cell-sorting and immunofluorescence-coupled RNA-FISH, we observed how neurons specifically show the multiple *trans* foci. We preliminarily observed a partial co-localization of the foci with stress-linked nuclear bodies. Testing different stresses, we find that neurons specifically increase Meg3 RNA levels upon low-dosage treatment with a genotoxic agent.

Laboratory members showed previously that transient overexpression of MEG3 activates a subset of p53-pathway genes in human cancer cells. This previous work pinpointed the structural features of the human MEG3 required for the p53-pathway activation (Uroda T. *et al.,* Molecular Cell, 2019).

We are currently exploring whether these features are conserved in the mouse lncRNA. To functionally study the stress-related Meg3 responses in neurons, we generated by CRISPR-Cas9 a set of mESC cell lines with different deletions in the Meg3 polycistron. Moreover, to gain a deeper understanding of the pathways influenced by Meg3 during stress responses, we are performing RNA hybridization capture experiments to identify putative lncRNA-interacting proteins. These will be validated by RNA-protein immunoprecipitation, and by dedicated functional assays. In summary, for the first time our study investigates the mechanisms through which a conserved imprinted lncRNA acts in post-mitotic cells (neurons) and following DNA damage induction.

Keywords: Meg3, lncRNA, genomic imprinting, DNA damage, stress, neurons

Biophysical models of the Zfp608 locus in mouse cells

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Abstract

Chromosome structural organization contributes to fundamental processes in the cell nucleus, including DNA transcription, replication, and repair. Experimental and theoretical works unveiled that chromosome spatial organization is a complex aggregate of layers: entire chromosomes occupy distinct volumes of the nucleus, called territories; regions of tens of Mega-bases (Mb) tend to organize in active and repressed (A/B) compartments; regions up to one Mb organize in domains (TADs); and loops may bring in contacts gene promoters with enhancers. However, the forces regulating these layers and their interplay with transcription activity are still elusive. Here, I will present an approach to studying these organizing principles in the genomic region around the Zfp608 gene in mouse embryonic stem cells, where the gene is transcriptionally inactive, and in neural progenitor cells (NPC), where it is active. By applying biophysical structural modeling, we focus on epigenomic-driven interactions between chromatin of the same type (e.g., active chromatin attracts other regions with the same chromatin marks), loop-extrusion dynamics, and the effect of promoter-enhancer interactions. Extensive quantitative analysis and comparison with Capture Hi-C data drives the models' parameterization. This project aims to show that biophysical models can help explain how experimentally observed structures are formed and unravel potential factors and molecular mechanisms regulating chromosome organization in different cell types.

Keywords: Biophysical 3D modelling, Capture HiC, Epigenetic mechanisms in development

ProA and ProB repeat sequences shape genome organization in human

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Abstract

In every eukaryotic cell, the genome is partitioned into two compartments, historically termed euchromatin and heterochromatin, but nowadays more often referred to as A and B compartments, with A favorable to gene expression and B unfavorable. There is a growing awareness that repeat sequences (RepSeq), which are the main constituents of the human genome, are also prime players in its organization.
We developed an unbiased strategy in order to identify DNA determinants of genome organization.
We identify sets of Repeat sequences (RepSeqs), both transposable elements (TE) and other types of repeats (non-TE), whose heterogeneous distribution along the genome is sufficient to quantitatively predict the genome partitioning profile between compartment A/euchromatin and B/heterochromatin.

Known properties of these sequences suggest that they are, actually, the main drivers of genome organization by functionally opposing each other, promoting the assembly and spreading of heterochromatin ("ProB elements") and opposing such spreading ("ProA elements"). Molecular mechanisms involved further generate self-reinforcement loops, forming a toggle-switch scheme that is assumed to be the foundation of A/B compartmentalization in every eukaryotic cell, irrespective of the exact nature of RepSeqs.

Whereas some RepSeqs are constitutively in a ProA or ProB state, others (or their derivatives), best known as gene regulatory elements ("enhancers"), can convert between states. Enhancers scattered along a chromatin domain and switching from a ProB to a ProA state appear to cooperatively unfold the domain, shifting it from B to A compartment and allowing gene expression. Enhancers can then act in a second way to promote gene expression, more directly influencing the activity of gene promoters by contact or proximity, as is now well known.

The genome of a eukaryotic cell thus appears as a realm populated and governed by and for RepSeqs, with gene regulation entirely depending on RepSeqs at all scales of genome organization.
Webinar = https://www.youtube.com/watch?v=8CIKaXSwceY

Keywords: repeat sequences, heterochromatin, enhancer

Epigenetic programming of the human sperm for embryonic development

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Abstract

In addition to paternal genetic information, the sperm provides to the embryo epigenetic cues. The nature and functional effect of this cues on embryo development are poorly understood. They could be necessary for a proper embryonic development and have an additional role in conveying the effect of the paternal environment onto the progeny. To unveil these potential roles, we are conducting an analysis focusing on histone post-translational modifications. We carried out an in-depth characterization of the landscape of modified histone in human sperm. Our study targets the largest set of human sperm histone features to date (H3K4me3; H3K9me3; H3K27me3; H3K36me3; H3K79me3; H3K9ac; H3K27ac, and H2A.Z) and use a calibrated ChIP-seq approach (ICe-ChIP seq: internal standard chromatin immune precipitation) to provide both the genomic location as well as the percentage of retained histone that harbor a histone modification at a given locus. Comparing the sperm ChiP-seq dataset with that from a hESC reference, we are able to pinpoint sperm-specific chromatin features. Additional investigations are under way to better understand how the sperm epigenome is shaped during spermatogenesis and to determine its fate in the embryo. Altogether this project will provide a comprehensive view of the human sperm histone PTMs landscape and help discriminate between the paternal epigenetic cues that are remnant of spermatogenesis from those likely to be involved in embryo development.

Keywords: Epigenetics, Histone modifications, ICe ChIP seq, Sperm, hESC, Transgenerational inheritance

A Scaffolding Element Rewires Local 3D Chromatin Architecture During Differentiation

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Abstract

Upon differentiation, chromatin rewires to reflect its new cellular identity and function. While it is widely known that this process involves cooperative changes in transcription, chromatin composition, and 3D conformation, it is unclear what exactly drives these changes and how they influence one another. Here, we used ESC-to-NPC differentiation to study rewiring at a 3 Mb large neuronal *Zfp608* locus. During this process, this large chromatin domain splits in half right at the *Zfp608* promoter, local chromatin gets littered with activating marks, compacts in 3D space and *Zfp608* abounds in transcription. We investigated the *cis* and *trans* elements using capture Hi-C (cHi-C), extensive biophysical modelling, and 3-colour 3D-FISH with technical and analytical breakthroughs and found that transcription abundance modulates the contacts in the region as well as the insulation at the domain split. Furthermore, we found a genetic element we named the scaffolding element, with a dual enhancer and architectural function that is essential for chromatin rewiring and loop formation at the NPC stage. The loss of this element disrupts the formation of all local NPC loops irrespective if they are anchored in this element or not, highlighting the hierarchical relationship between elements that act as loop anchors. Furthermore, we uncovered that the scaffolding function, although driven by multiple mechanisms, can form loops independent of loop-extrusion and that other molecular attractions were necessary to form NPC-specific contacts in the region. Together, these results demonstrate that a hierarchy of genetic elements in *cis* allows successful rewiring during differentiation and that multiple *trans* acting elements contribute to making this rewiring efficient.

Keywords: chromatin, 3D chromatin conformation, insulation, gene regulation, enhancers, differentiation, ESC, NPC

CRISPR screens to discover new regulators of genomic imprinting

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Abstract

More than 100 genes in the human and mouse genomes are mono-allelically expressed upon their parent-of-origin. This phenomenon, namely genomic imprinting, is based on sex-specific differential methylation of regulatory DNA sequences. Genomic imprinting is involved in a variety of biological processes, ranging from development to metabolism. Although imprints have arisen a great interest in the last years, the mechanism of silencing of the methylated allele is scarcely known. My project aims at discovering new trans-acting regulators of genomic imprinting. For that purpose, I performed different genome wide pooled CRISPR screens using a reporter allele of the endogenous maternally imprinted gene Peg3 in primary mouse embryonic fibroblasts.

Keywords: epigenetic regulation, methylation, inheritance

RNA profiling of molecular crowed nuclear micro-environments

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Abstract

Studying nuclear micro-environments, particularly membrane-less organelles (MLO) such as Cajal bodies, PML bodies, speckles, and paraspeckles, has always been a challenge. Indeed, such MLO display a high molecular crowding which typically result from liquid-liquid phase separation. However, the isolation of such liquid-like droplets and the characterization of their internal components is key to understand their roles.
In a prior study, our team showed that high-salt concentrations can insolubilize these crowded nuclear micro-environments, allowing their separation from other soluble nuclear components. This method enables the identification of "High-salt Recovered Sequences" (HRS), genomic DNA sequences enriched in the insolubilized nuclear micro-environments compared to the soluble fraction. In mouse embryonic stem cells, HRS have been associated with the active A chromosomal compartment, including transcription start sites, enhancers of highly expressed genes, and known MLOs like Cajal bodies, speckles, and paraspeckles (Baudement et al. 2018).

Here, we have evolved this method to recover both RNA and genomic DNA in IMR-90 cells (human embryonic lung fibroblasts), allowing us to perform the first global profiling of RNA transcripts associated with highly crowded nuclear micro-environments. We found that these transcripts largely consist of specific long non-coding RNAs (lncRNAs), some of which are already known to be associated with specific nuclear bodies, such as Neat1_2, an architectural RNA of paraspeckles. Moreover, premature RNA transcripts were significantly more enriched in the insoluble RNA fraction compared to their mature counterparts. Finally, transcripts with specific intron retention events were also found to be enriched, including one that is dependent on paraspeckle integrity.
We plan to apply RNA interference in IMR-90 cells to disrupt paraspeckles and further use this method to analyze the global RNA and genomic DNA content within these MLOs. This approach could be extended to various MLOs to deepen our understanding of their roles within the nucleus.

Keywords: Chromatin, Phase separation, RNA, Nuclear bodies

Nuclear Ythdc1 is the cytoplasmic m6A reader for maternal mRNA decay during the maternal-to-zygotic transition

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Abstract

N6-methyladenosine (m6A) is the most abundant mRNA modification in eukaryotes. The pathway involves a methyltransferase complex (writers) and proteins that bind m6A and impact mRNA fate (readers). The methylation m6A regulates a wide range of biological processes, in particular the maternal-to-zygotic transition (MZT) during early embryogenesis. The MZT consists in the massive degradation of maternal mRNAs and the zygotic genome activation. Maternal mRNA degradation depends on two pathways, one maternal that involves maternally deposited molecules, and one zygotic based on zygotically produced components. Among m6A readers, Ythdf types are cytoplasmic, whereas Ythdc are rather nuclear. Here, we address the implication of m6A in maternal mRNA decay in *Drosophila* embryos. We show that the m6A writers, Mettl3 and Mettl14, are expressed in ovaries and required for m6A methylation of maternal mRNAs. Using RNA-seq, we find that the loss of function of Mettl3 and Mettl14 affects maternal mRNA degradation in embryos and that both proteins are involved in the maternal pathway of mRNA decay. Strikingly, we find that both m6A readers, Ythdf and Ythdc1, are deposited maternally in embryos and that although Ythdc1 is nuclear in somatic cells, it is cytoplasmic in early embryos. Furthermore, based on mRNA decay in *Ythdf* and *Ythdc1* mutant embryos, we identify Ythdc1 as the main m6A reader for maternal mRNA decay. Ythdc1 is in complex and colocalizes with the RNA binding protein Smaug, a major actor of maternal mRNA decay in *Drosophila* embryos. These results reveal a cytoplasmic function of Ythdc1 during early embryogenesis and shed light on connections between m6A and other pathways of mRNA decay.

Keywords: m6A methylation, Ythdc1, maternal mRNA decay, Drosophila

Mechanistical investigation of X-chromosome reactivation in the germline

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Abstract

During mammalian embryogenesis, specific chromatin epigenetic marks, such as histone modifications and DNA methylation, are acquired. These determine gene expression and maintain cell identity of the different lineages. Among these epigenetic changes, transcriptional inactivation of one of the two X chromosomes occurs in females by a process called X-chromosome inactivation (XCI). This is established and clonally propagated in female somatic cells to ensure gene dosage balance compared to males.
Exceptionally, gamete precursors, the primordial germ cells (PGCs), undergo profound global epigenetic remodeling to ultimately acquire competency to form the germline and express germline-specific genes. Reprogramming includes genome-wide DNA demethylation, redistribution of histone marks, erasure of genomic imprints, and, in females, X-chromosome reactivation (XCR). XCR involves the loss of coating of the long non-coding RNA Xist, DNA demethylation at promoters and re-expression of X-linked genes from the Xi.

Although XCI –*in vivo* and *in vitro*– has been well studied, how XCR is regulated in PGCs and its biological impact –i.e. in X pairing and/or synapsis during meiosis– remains largely unknown. In our lab, we have recently contributed to the understanding of how XCR is established during PGCs specification *in vivo* (Roidor, Syx et al 2023).
Now, we aim to dissect the regulatory mechanisms underlying XCR. To achieve this, we have generated a unique culture-based PGC-like cell (PGCLCs) system, carrying a fluorescent reporter for XCR, an inducible XCI system, and allele-specific information. To unveil the major contributors to XCR during *in vitro* PGCLCs specification, we combined our system with: 1. Genome-wide CRISPR-gene screening, and 2. candidate-based approaches. This novel model allows us to study sex-specific reprogramming during germline differentiation, advancing our understanding of the epigenetic mechanisms behind this process, as well as the influence of XCR on gametes formation.

Keywords: germline, X, chromosome reactivation (XCR), gene regulation, embryo development, genome, wide CRISPR screen

A histone hyperacetylation pulse induces cellular memory of 3D genome folding and gene regulation

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Abstract

Cellular identity is defined by the expression of specific gene sets. Once established, it is maintained through alternative chromatin states, which are propagated through cell divisions. While epigenetic systems can assign alternative activity states to the same DNA sequence, cellular memory refers to mechanisms that maintain these sustained cellular states in response to transient stimuli. Although the two mechanisms are inherently linked, it is currently unclear which epigenetic regulators have also a role in cellular memory. To study the role of cellular memory, we subjected mouse embryonic stem cells (mESCs) to a transient chromatin perturbation that disrupts the epigenome and chromosome conformation. Specifically, we studied how chromatin architecture changes when histone acetylation is perturbed by treating cells with the histone deacetylase inhibitor TSA. We obtained ultra-deep contact maps which entail at least 6 billion unique contacts per condition. Besides changing short range chromatin folding by causing decondensation and differential looping, TSA treatment equally affects long-range architecture, where contacts between open chromatin regions decrease, and new contacts form between chromosomes. Strikingly, while the histone landscape and gene expression are rapidly restored following TSA removal, chromatin architecture is slower to rescue and retains a partial memory of its perturbed state even through cell division. This is significant, as when cells are re-exposed to the same perturbation recovery is less complete, indicating the activation of cellular memory. We find that this sustained gene de-regulation is linked to strong enhancer-promoter contacts and Polycomb-mediated repressive loops that perpetuate alternative activity states. Thus, these results identify a novel role for 3D genome folding in cellular memory.

Keywords: Genome folding, cellular memory, chromatin states, Polycomb, embryonic stem cells

DNA methylation regulation during development and posterior regeneration in the annelid Platynereis dumerilii.

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Abstract

Changes in cell identity, an essential process for embryogenesis and regeneration, require massive variations in gene expression. Epigenetic marks, such as m5C DNA methylation, have been well described in mammalian models for their role in modulating gene transcription and lineage commitment. However, data on the involvement of these epigenetic machineries in cell fate decisions during regeneration and in unconventional organisms are scarce.
The marine annelid *Platynereis dumerilii* is a suitable non-mammalian model to study the role of m5C methylation during developmental processes. Indeed, previous work in our team showed a high level of global m5C methylation, similar to that in vertebrates, and a dynamic expression of its associated machinery, throughout *Platynereis'* lifecycle. Furthermore, treatments using decitabine (a hypomethylating agent) impacts both its development and its posterior regeneration.

Building on these findings, I aim to provide a more detailed description of m5C variations at the gene level, using Whole Genome Bisulfite Sequencing (WGBS) for various stages of development and for various stages of the posterior regeneration. This will provide a better understanding of how the epigenome influences gene expression and cell fate.
Furthermore, as decitabine affects a population of stem cells essential for the continuous growth of the animals, we are investigating the reformation of this population during regeneration from a panel of signature genes. Hypomethylation of the latter alters the stem cells' ability to produce differentiated cell lineages, we are interested in how m5C methylation impacts both their regulation and thereby the formation of the new tissues. To this end, I am performing WGBS on regenerated structures from decitabine-treated samples versus controls. On the one hand, we will look at the impact of this pharmacological agent during regeneration when the stem cell population is reformed. Concurrently, we will examine the long-term impact, after treatment cessation, on the newly formed tissues.

Keywords: Epigenetic, DNA methylation, regeneration, annelid

Non-canonical roles of the Polycomb PRC1 complex in its tumor suppressor function

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Abstract

Polycomb Group Proteins (PcGs) are epigenetic repressors that form two main complexes – PRC2 and PRC1 –collaborating to stably repress their target genes, thereby establishing a cellular memory of their transcriptional state.
In the embryo, PRC2 and PRC1, as well as their respective histone marks, H3K27me3 and H2AK118ub, colocalize on approximatively 200 genes.

However, PcG proteins are also involved in dynamic processes. After demonstrating that only the loss-of-function of PRC1, but not of PRC2, led to the generation of tumors, the team demonstrated the existence of a functional uncoupling between PRCs complexes at the larval stage, PRC1 being recruited in the absence of the H3K27me3 mark on a thousand targets called neo-PRC1 genes, characterized by a high transcriptional level of expression and an enrichment in ontologies known to be deregulated in cancer.
In order to unravel the non-canonical pathways of Polycomb-mediated gene regulation and its implication in cancer, we implemented an approach combining an in silico study with an in vivo functional genetic screen, which allowed us to identify two substoichiometric interactors of PRC1. One is FOXO, the fly ortholog of mammalian FOXO3, a pioneer factor associated with cancer in human. The second one is EcR, the nuclear receptor of the Ecdysone pathway. Our data suggest that they as act on distinct target genes. Furthermore, transcriptomic and genomic studies suggest a co-suppressor role of FOXO and PRC1, in contrast to EcR, which appears to be a co-activator of PRC1. All these results converge towards the existence of a dynamic control of PRC1 during development that fine-tunes the balance between proliferation and differentiation during the phase of intense tissue growth specific to the larval stage.

Keywords: Polycomb, Drosophila, cancer, pioneer factor FOXO

Cornelia de Lange syndrome, a cell senescence and polycomb related developmental disease

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Abstract

Cornelia de Lange Syndrome (CdLS) largely caused by mutation of the cohesin DNA loader NIPBL is a rare multi-organ developmental disorder left without any therapeutic strategy.
To faithfully mimic the disease and to identify a therapy, we generated a novel C57Bl/6J *Nipbl*-haplo-insufficient mouse model of the disease. Under this genetic background the mice recapitulate many of the defects observed in CdLS patients. These mice featured a severe growth delay. *Nipbl+/-* embryonic and neonatal hearts developed ventricular hypertrophy, aortic and valve defects associated with a persistent truncus arteriosus and a ventricular septal defect. Neck, face and oesophagal muscles derived from the embryonic second heart field were less developped in *Nipbl+/-* than in wt embryos.

We also used human iPS (induced pluripotent stem cells) derived from CdlS patients. Cells were differentiated in smooth muscle cells. CdlS patient cells smooth muscle cells feature cell senescence.

Using proteomics and RNA-sequencing, we identified a dysregulated TGFb pathway in the outflow tract of embryonic hearts. We found senescent cells in *Nipbl+/-* embryonic hearts, limb primordium cartilage and in post-natal tissues including muscle and brain cortex. Treatment of pregnant *Nipbl+/-* mice with a TGFbR inhibitor (galunisertib) prevented cell senescence and rescued both the cardiac phenotype and the size of mice at birth. The drug used in oncology also blocked senescence of IPS cell-derived smooth muscle cells from CdLS patients. Anti-Ezh2 and h3K27me3 ChiP revealed an absence of occupation of both the polycomb and the epigenetic mark on cdnk1a genomic regulatory regions in CdlS-patient IPS cell-derived smooth muscle cells .
Altogether we report that an exacerbated TGFb pathway and a deficient polycomb-mediated epigenetic program associated with embryonic programmed cell senescence is responsible for many defects in a CdLS mouse model.

Keywords: cohesin, cell senescence, polycomb

The coupling between epigenetic regulation, chromatine configuration and liquid-liquid phase separation

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Abstract

Recent experimental and theoretical evidences suggest that the formation of 3D chromatin compartments and their impact on gene regulation is linked to the property of architectural proteins to undergo liquid-liquid phase separation (LLPS), ie to drive the formation of protein condensates in where specific chromatin regions but also many histone modifying enzymes (HMEs) and transcription factors will localize to. While the biophysics of LLPS and the mechanisms driving genome folding start to be well characterized separately, the coupling between both remains unclear. In collaboration with the group of Giacomo Cavalli (IGH), we are addressing that question in the context of Polycomb bodies in Drosophila embryos. Using polymer modeling, we investigate systematically the key biophysical parameters that may drive the formation of such nano-scale condensates. Preliminary data suggest an important role of PRC1-PRC1 self-attraction and of PRC1-chromatin interactions.

Keywords: epigenetic regulation, chromatine configuration, liquid liquid phase separation, Monte Carlo simulation

Role of the maternal-effect Padi6 gene in epigenetic reprogramming and zygotic genome activation of mouse embryos

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Abstract

PADI6 belongs to the multi-protein sub-cortical maternal complex (SCMC) that is present specifically in mammalian oocytes and early embryos. Maternal inactivation of SCMC genes generally results in early embryo lethality. In humans, variants in a subset of SCMC genes have been found in the healthy mothers of children affected by genomic imprinting disorders and characterized by multi-locus imprinting disturbances (MLID). However, how the SCMC controls the DNA methylation required to regulate imprinting remains poorly defined. To address this issue, we generated a mouse line carrying a *Padi6* missense variant that had been identified in the mother of two sisters affected by Beckwith-Wiedemann syndrome and MLID. We found that if homozygous in female mice this variant resulted in interruption of embryo development at the 2-cell stage. Single-cell DNA methylation and RNA analyses demonstrated genomic hypermethylation, down-regulation of zygotic genome activation (ZGA) genes and up-regulation of maternal decay genes in 2-cell embryos from homozygous females. In addition, immunofluorescence analysis showed abnormal localization of DNMT1 and UHRF1 in mutant oocytes and zygotes. Taken together, this study demonstrates that PADI6 controls the subcellular localization of DNMT1 that is necessary for pre-implantation epigenetic reprogramming and ZGA.

Keywords: Genomic imprinting, Maternal, effect genes, Epigenetic reprogramming

Transcriptional and chromatin landscapes of the inactive X-chromosome in the germline

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Abstract

Primordial germ cells (PGCs) give rise to future gametes which are crucial to transmit genetic and epigenetic information to the next generation. In mice, PGCs undergo a global epigenetic reprogramming process, such as DNA demethylation, histone marks reshuffling, erasure of genomic imprinting, in both sexes and the reactivation of the inactive X chromosome (Xi) in females. This reactivation leads to an excess of X-linked gene products in females compared to males and could play a role in sex dimorphism and gametogenesis. The reactivation is marked by the re-expression of X-linked genes and the loss of repressive chromatin marks (H3K27me3).
The laboratory showed that in early PGCs the Xi is progressively reactivated during development. Different genes follow distinct reactivation kinetics along the Xi, with some genes always reactivating earlier than others just before meiosis entrance and sex gonadal differentiation.

We are exploring what triggers some X-linked genes to reactivate earlier than others and whether this can be explained by different epigenetic landscapes such as histone marks, and DNA methylation.

To answer these questions, I use *in vivo* approaches in mice, complemented by sophisticated genetics, and low-input epigenomic profiling to dissect female epigenetic reprogramming in the germline.

We are studying female PGCs to correlate the expression and enrichment in H3K27me3 and DNA methylation. We generate a histone marks map to analyse enrichment changes between active versus inactive X chromosomes over time. Interestingly, we observed differential H3K27me3 enrichment for genes with different reactivation kinetics.
Moreover, these results will allow us to address whether germline epigenetic reprogramming progresses similarly on autosomes and sexual chromosomes in both sexes. This will enhance our understanding of the impact of X-chromosome reactivation on cancer and reproductive health.

Keywords: X, chromosome reactivation, primordial germ cells, reprogramming, epigenomic

Nuclear Organisation of Transcription Factors and Epigenetic Marks guiding Embryo Development

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Abstract

During embryonic development, morphogenesis occurs, as indicated by the defined body axes through signaling patterns from developmental genes (Hartenstein, 1993; Krotov et al., 2014; Petkova et al., 2019). This process transforms a spatially uniform fertilized egg into a segmented body. Notably, we have observed increased heterogeneity in the sub-nuclear distributions of key transcription factors (TFs) like Hunchback and Krüppel, as well as histone modifications during the same period (Tsai & Crocker, 2022). This observation suggests that TF distributions during different developmental stages may undergo a morphogenic process reflective of the underlying nuclear architecture.

My project aims to test the hypothesis that TF distributions mirror underlying chromatin architecture during development. To achieve this, we plan to image up to 5 additional TFs with varying expression windows, using immunofluorescence in fixed embryos and high-resolution imaging techniques available at the CRBM, Montpellier. Spatial correlations and topological analysis will be applied to extract quantitative metrics of TF distributions. Comparison with epigenetic marks from prior imaging data will assess congruence. Our goal is to observe a transition from uniform to heterogeneous TF distributions across development. Composite time-courses will be constructed to compare nuclear developmental patterns in distinct cell lineages. This proof-of-principle study lays the foundation for a systematic survey of TF and epigenetic mark spatial organization, shedding light on how embryo development reshapes the nucleus. Ultimately, the results will clarify if nuclear development parallels animal body morphogenesis at both macroscopic and microscopic scales.

Keywords: Nuclear Morphogenesis, Transcription Factors, Epigenetic Marks, Heterogenity, Super, Resolution Microscopy, Spatial Correlation

The RNA binding activity of the Drosophila Hox Transcription Factor Ultrabithorax contributes to muscle morphogenesis in developing embryos

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Abstract

Transcription factors (TFs) orchestrate tissue development and maintenance by controlling different molecular layers of gene programs. Beyond their function on DNA, TFs also interact with RNA and regulate mRNA splicing. Yet, a large gap remains in understanding TF-RNA regulatory function and its significance for tissue morphogenesis. Previous work in our lab demonstrated that the Hox TF Ultrabithorax (Ubx) binds RNA and regulates alternative splicing. Moreover, Ubx genetically interacts with several splicing factors including the small nuclear ribonucleoprotein snRNPU1-70K to regulate embryonic muscle development. Yet, the significance of Ubx-RNA interaction in morphogenesis is unknown. My PhD project investigates this issue. Relying on Ubx/snRNPU1-70K genetic interaction in somatic musculature of Drosophila embryos, we assessed the ability of different DNA/RNA binding Ubx mutants to rescue the muscle alteration. Moreover, we evaluated the global function of Ubx DNA/RNA binding mutants in the Ubx null homozygous mutant context. This indicates that Ubx-RNA binding activity contributes to its homeotic function. Presently, I am investigating Ubx-splicing function in vivo in muscle cells by employing single-molecule fluorescence in situ hybridization (smFISH) to detect the expression of exon RNAs differentially spliced by Ubx. Altogether, these results uncovered the significance of Ubx-RNA activity in myogenesis. In future, this work will provide new insight into the contribution of Ubx-splicing function in muscle morphogenesis.

Keywords: Transcription factor, splicing function, morphogenesis, RNA binding ability, Hox

Identifying how cell-type-specific distal regulatory elements orchestrate the EMT initiation

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Abstract

During the epithelial-to-mesenchymal transition (EMT), epithelial cells acquire a more migratory, invasive, and apoptosis-resistant state. While this process is crucial during embryogenesis and tumor metastasis, its molecular mechanisms at the chromatin level have yet to be determined.
Distal regulatory elements, such as enhancers, provide a spatio-temporal control of gene expression. Their cell-type-specific activation is due to a subset of transcription factors termed pioneer factors, which can associate with nucleosomal or heterochromatic DNA to initiate their activation and thus affect cell identity establishment.

Using an inducible cellular model recapitulating the EMT of human mammary epithelial cells, we have identified subsets of cell-type-specific enhancers that undergo massive chromatin changes within the first 24 hours of EMT initiation. We also identify strong candidate actors of this EMT regulatory pendulum using a bioinformatics pipeline. TP63 is the epithelial-cell state pioneer factor, while the AP-1 complex seems to act as a priming or bookmarking pioneer factor to indicate mesenchymal-specific enhancers in epithelial cells and jumpstart their activation upon EMT initiation.
Going forward, our goal is to investigate the activity switch of the mesenchymal-specific enhancers' upon EMT initiation to provide an understanding of how enhancers regulate cell determinism and the significance of these mechanisms in cancer.

Keywords: Epithelial to Mesenchymal Transition, Enhancers, Transcriptional Regulation, Pioneer Factors

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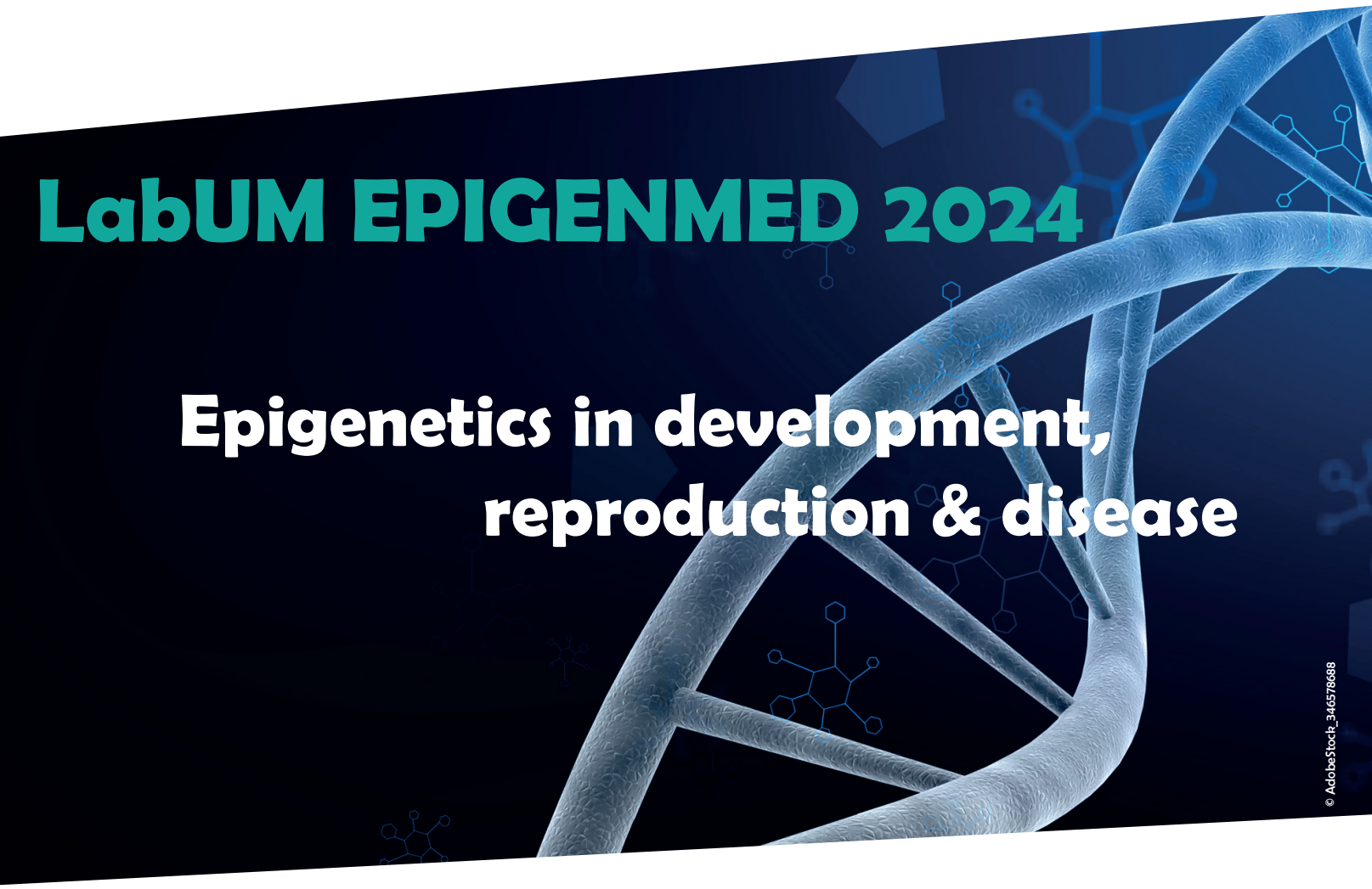

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