

EPIGENETIC INHERITANCE SYMPOSIUM 2021

Impact for Biology and Society

25–27 August 2021
ETH Zurich, Switzerland



Universität
Zürich^{UZH}

ETH zürich



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Important information

Zoom link to the talks:

<https://ethz.zoom.us/j/7861711735>



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on Twitter #eis21

Summary of the previous edition

Symposium summary: Epigenetic inheritance—impact for biology and society 26–28 August 2019, Zurich, Switzerland,

Irina Lazar–Contes, Martin Roszkowski, Deepak K Tanwar, Isabelle M Mansuy.



Environmental Epigenetics
Volume 6, Issue 1, 2020,
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[https://doi.org/10.1093/eep/
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WELCOME



Dear colleague, student and friend,

It is a great pleasure to welcome you to the 2021 Epigenetic Inheritance Zurich symposium as a follow-up of the 2017 and 2019 editions of the symposium. This year, the meeting will be fully online due to the current Covid-related restrictions. But as the previous editions, it will feature important aspects of epigenetic inheritance across different disciplines, from genetics/epigenetics to metabolism, behavioral science, RNA biology, toxicology, single cell omics and bioinformatics in humans and various animal models.

It will discuss new findings and discoveries, highlight challenges of the discipline and reflect on perspectives for biology, medical research and the society. It will offer keynote lectures from leaders in the field, short flash talks and a workshop "Meet the Experts".

I hope that you'll enjoy the symposium and find it inspiring for your research and your thinking about the biology of heredity. I wish you a great and productive time and warmly thank you for participating.

Isabelle Mansuy

PROGRAM

Wednesday 25.08.2021

Introduction

14:00–14:10 (CET) *Isabelle Mansuy, Professor in Neuroepigenetics, University and ETH Zurich*

Session 1

Environmental epigenetics

Chair: Isabelle Mansuy, University and ETH Zurich, CH

- 14:10–14:50 *Cecilie Svanes, University of Bergen, Norway*
Epidemiological studies of exposures during the pre-puberty period and future offspring health.
- 14:50–15:30 *Adam Watkins, University of Nottingham, UK*
Paternal programming of offspring development and ill-health.
- 15:30–16:10 *Jordana Bell, Kings College London, UK*
Genetic impacts on human methylome variation.
- 16:10–16:30 *Break*
- 16:30–17:10 *Emilie Rissman, North Carolina State University, USA*
Transgenerational actions of BPA on behavior and synapses.
- 17:10–17:50 *Michael Skinner, Washington State University, USA*
Environmentally-induced epigenetic transgenerational inheritance of pathology: Systems epigenetic disease etiology and generational toxicology.

PROGRAM

Thursday 26.08.2021

Session 2

The power of single cell approaches
Chair: Isabelle Mansuy, University and ETH Zurich, CH

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|-------------------|---|
| 14:00–14:40 (CET) | <i>Fuchou Tang, Beijing Advanced Innovation Center for Genomics, Peking University, China</i> <i>Decoding the epigenetic regulation of human germline cell development by single cell genomics approaches.</i> |
| 14:40–15:20 | <i>Gavin Kelsey, The Babraham Institute, UK</i> <i>Intergenerational impact of maternal high-fat diet – A single-cell analysis.</i> |
| 15:20–15:30 | <i>A piece of art by Sandrine Donnio Renaud</i> |
| 15:30–15:45 | <i>Break</i> |
| 15:45–16:25 | <i>Wolf Reik, The Babraham Institute, UK</i> <i>Single cell multi-omics landscape of development and ageing. (Talk recorded).</i> |
| 16:25–16:40 | <i>Kai Kleber, Dovetails</i> <i>HiChIP and promoter capture Hi-C: Using MNase-based kits to investigate transcriptional control.</i> |

Workshop

| | |
|-------------|--|
| 17:00–18:30 | «Meet the experts: Questions and Answers» <i>Noora Kotaja, Gavin Kelsey and Michael Skinner.</i> <i>Moderator: Rodrigo Arzate-Meija, Laboratory of Neuroepigenetics, University and ETH Zurich</i> |
|-------------|--|

PROGRAM

Friday 27.08.2021

Session 3

Mechanisms

Chair: Isabelle Mansuy, University and ETH Zurich, CH

14:00–14:40 (CET) Noora Kotaja, University of Turku, Finland

Germline RNAs in the control of male fertility and epigenetic inheritance of diet-induced metabolic conditions.

14:40–15:20 Anita Öst, Linköping University, Sweden

Small RNAs transmit big epigenetic message: Intergenerational reprogramming of metabolism.

15:20–15:30 *Break*

15:30–15:45 Bermans Iskandar, University of Wisconsin, USA

Transgenerational disruption of DNA methylation marks by ancestral folate supplementation is associated with enhanced axonal regeneration.

15:45–16:00 Anara Alshabayeva, University and ETH Zurich, Switzerland

Circulating extracellular vesicles are vectors of communication with the germline that play a role in epigenetic inheritance

16:00–16:40 Brett Nixon, University of Newcastle, Australia

The role of the epididymis in linking paternal exposures to alteration of the sperm epigenome (Talk recorded).



"Lignée transgénérationnelle"

by Sandrine Donnio Renaud

<https://www.sandrinedonnio Renaud.com/>

SPEAKERS

Epidemiological studies of exposures during the pre-puberty period and future offspring health.

Cecilie Svanes, University of Bergen, Norway

Abstract

Emerging evidence suggests that exposures in pre-puberty, particularly in fathers-to-be, may impact the phenotype of future offspring. Analyses of the RHINESSA cohort find that offspring of father's exposed to tobacco smoking or overweight that started in pre-puberty demonstrate poorer respiratory health in terms of more asthma and lower lung function. A role of pre-puberty onset smoking for offspring fat mass is suggested in the RHINESSA and ALSPAC cohorts, and historic studies suggest that ancestral nutrition during pre-puberty play a role for grand-offspring health and morbidity. Support for causal relationships between ancestral exposures and (grand-)offspring health in humans has been enhanced by advancements in statistical analyses that optimize the gain while accounting for the many complexities and deficiencies in human multi-generation data. The biological mechanisms underlying such observations have been explored in experimental models. A role of sperm small RNA in the transmission of paternal exposures to offspring phenotypes has been established, and chemical exposures and overweight have been shown to influence epigenetic programming in germ cells. For example, exposure of adolescent male mice to smoking led to differences in offspring weight and alterations in small RNAs in the spermatozoa of the exposed fathers. It is plausible that male pre-puberty may be a time window of particular susceptibility, given the extensive epigenetic reprogramming taking place in the spermatocyte precursors at this age. In conclusion, epidemiological studies in humans, mechanistic research and biological plausibility, all support the notion that exposures in the pre-puberty of males may influence the phenotype of future offspring.



Paternal programming of offspring development and ill-health.

Adam Watkins, University of Nottingham, UK

Abstract

Studies have now identified strong associations between patterns of growth during fetal and neonatal life and an increase predisposition toward developing cardio-metabolic diseases in adult life. Whilst the connection between a mother's diet and the long-term health of her offspring has been studied in detail, our understanding of the paternal programming of offspring health is comparatively limited. Disturbances in paternal reproductive epigenetic status represent one key mechanism linking paternal diet with the programming of offspring development and adult health. Here poor paternal nutrition could result in perturbed sperm and testicular epigenetic status as many enzymatic processes involved in epigenetic regulation use metabolic intermediates to modify DNA and histones. Perturbed sperm and testicular epigenetic status have the potential to modify post-fertilisation gene transcriptional regulation and protein expression in offspring tissues, resulting in increased incidences of metabolic disorder in adult life. In addition, studies suggest a sophisticated role for the seminal plasma in the modulation of the maternal uterine periconception cell-signalling, inflammatory and immunological physiology. These seminal plasma effects on the maternal periconception environment act to facilitate uterine remodelling, embryo implantation and fetal development. Evidence is now emerging that poor paternal lifestyle factors such as diet, can also modify these essential uterine responses, altering fetal development and ultimately long-term offspring health.



SPEAKERS

Genetic impacts on human methylome variation.

Jordana Bell, Kings College London, UK

Abstract

Studies of the human methylome have identified multiple drivers of DNA methylation variability. An overview of the extent of human methylome variation that is estimated to be under genetic control will be presented, based on recent large-scale efforts from multiple international cohorts. This will be followed by recent results from twin-based and UK population cohort-based analyses identifying an enrichment of local genetic impacts on DNA methylation at enhancers, profiled on the Illumina Infinium MethylationEPIC BeadChip. Summary-based Mendelian Randomization analysis exploring the relationship between DNA methylation and human phenotypes identified a series of co-localisation events, suggesting potential pleiotropic effects. Identifying genetic impacts on DNA methylation can improve our understanding of pathways that underlie gene regulation and disease risk.



Transgenerational actions of BPA on behavior and synapses.

Emilie Rissman, North Carolina State University, USA

Abstract

Endocrine disrupting chemicals (EDCs) are ubiquitous in the environment and present in human urine and blood. Data on one EDC (Bisphenol A, BPA) has raised enough concern about actions on human health that it has been removed from plastics used to contain food, but similar untested compounds are being used as substitutes. We used rodent models to examine transgenerational effects of BPA on behavior. We demonstrated transgenerational, third (F3) and fourth (F4) generational effects of BPA exposure during gestation on a number of social behaviors in C57BL/6 mice. We examined mechanisms that underlie behavioral phenotypes starting with an RNA-sequencing (seq) study on brain tissues from F3 mice. BPA has been shown to change expression of imprinted genes, thus we examined gene expression and DNA methylation in imprinted genes. We found changes in expression of maternally expressed gene 3, Meg3, at various ages and regions of F3 brains. But we did not find any differences in DNA methylation either in the differentially methylated region (DMR) or the gene promoter of Meg3. Next, we selected a set of target genes present in post-synaptic densities (PSD). Using qPCR we confirmed a significant difference in expression in F3 brains from control and BPA-lineages particularly in brains collected the day after birth. To complete this set of experiments we used F1 brains, interrogated the same set of genes, and found the same pattern of expression. These data implicate genes that are candidates for autism.



SPEAKERS

Environmentally-induced epigenetic transgenerational inheritance of pathology: Systems epigenetic disease etiology and generational toxicology.

Michael Skinner, Washington State University, USA

Abstract

Transgenerational effects of environmental toxicants significantly amplify the biological impacts and health hazards of these exposures. One of the most sensitive periods to exposure is during fetal gonadal sex determination when the germ line is undergoing epigenetic programming and DNA re-methylation occurs. Previous studies have shown that toxicants (e.g. Glyphosate) can cause an increase in adult onset disease such as infertility, prostate, ovary and kidney disease, cancers and obesity. Interestingly, this effect is transgenerational (F1, F2, F3 and F4 generations) due to permanent (imprinted) epimutations in the germline. The transgenerational epigenetic mechanism appears to involve the actions of an environmental compound at the time of sex determination to permanently alter the epigenetic (e.g. DNA methylation) programming of the germ line that then alters the transcriptomes of developing organs to induce disease susceptibility and development transgenerationally. In addition to DNA methylation, alterations in sperm ncRNAs and histone retention have also been observed. A variety of different environmental compounds have been shown to induce this epigenetic transgenerational inheritance of disease including: fungicide vinclozolin, plastics BPA and phthalates, pesticides, DDT, dioxin, hydrocarbons and herbicides like atrazine and glyphosate. Interestingly, exposure specific epigenetic alterations were observed between the specific toxicants. The suggestion is that environmental toxicants can reprogram the germ line to induce epigenetic transgenerational inheritance of disease, which is a new paradigm in disease etiology, and indicates generational toxicology needs to be assessed in the future. A systems epigenetic analysis of the various exposures identified specific molecular impacts on distinct subsets of specific disease associated genes. Observations reveal a novel concept for disease etiology that incorporates environmental epigenetics.

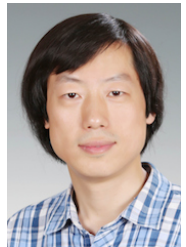


Decoding the epigenetic regulation of human germline cell development by single cell genomics approaches.

Fuchou Tang, Beijing Advanced Innovation Center for Genomics, Peking University, China

Abstract

Mitochondrial DNA (mtDNA) mutations are often associated with incurable diseases and lead to live birth defects in 1 out of 200 babies. Uncoupling of the inheritance of mtDNA and the nuclear genome by spindle transfer (ST) can potentially prevent the transmission of mtDNA mutations from mother to offspring. However, no well-established studies have critically assessed the safety of this technique. Using single-cell triple omics sequencing method, we systematically analyzed the genome (copy number variation), DNA methylome, and transcriptome of ST and intracytoplasmic sperm injection (ICSI) control blastocysts. We will discuss the epigenetic similarities and differences between the ST and control blastocysts.



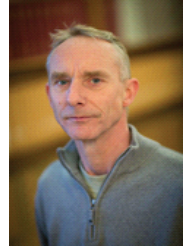
SPEAKERS

Intergenerational impact of maternal high-fat diet – A single-cell analysis.

Gavin Kelsey, The Babraham Institute, UK

Abstract

Over the life course, the mammalian genome undergoes profound setting and resetting of epigenetic information. Germ-cell specification, gametogenesis, and early embryo development are characterised by phases of widespread erasure and rewriting of DNA methylation. This extensive reprogramming largely prevents transmission of epigenetic information across generations; however, reprogramming events must ensure both correct zygotic genome activation, and locus-specific persistence of gamete-derived methylation as in the case of genomic imprinting. This underscores the importance of understanding how methylation patterns are established in the germline and the extent to which they may be influenced by adverse physiological or environmental factors, or procedures applied in assisted reproduction. Our mechanistic studies have identified gene transcription as top of a hierarchy of events that pattern the oocyte epigenome; this is important, as it predicts that changes in gene expression in the oocyte resulting from adverse maternal physiology or exposure will have direct consequences on the epigenome. We recently pioneered genome-wide joint profiling of DNA methylation, gene expression and chromatin accessibility. We are deploying these capabilities to explore effects of maternal diet on the epigenetic quality of the oocyte, and to investigate whether anomalies detected persist in the embryo.



Single cell multi-omics landscape of development and ageing. (Talk recorded).

Wolf Reik, The Babraham Institute, UK

Abstract

Epigenetic information is relatively stable in somatic cells but is reprogrammed on a genome wide scale in germ cells and early embryos. Reprogramming is essential for imprinting, the return to naïve pluripotency, the erasure of epimutations, and for the control of transposons. Following reprogramming, epigenetic marking occurs prior to and during lineage commitment in the embryo. The epigenome changes in a potentially programmed fashion during the ageing process; this epigenetic ageing clock seems to be conserved in mammals. Our work addresses the mechanisms and consequences of global epigenetic reprogramming in the germ line and at zygotic genome activation. Using single cell multi-omics techniques, we are beginning to chart the epigenetic and transcriptional dynamics and heterogeneity during the exit from pluripotency and initial cell fate decisions leading up to gastrulation. We discovered priming of enhancers prior to lineage decisions as well as acute epigenetic remodeling of enhancers at the time of lineage commitment. We are also interested in the programmed degradation of epigenetic information during the ageing process, how this might be coordinated across tissues and individual cells, and how this process potentially could be reversed.



SPEAKERS

HiChIP and promoter capture Hi-C: Using MNase-based kits to investigate transcriptional control.

Kai Kleber, Dovetails Genomics, UK

Abstract

Chromatin conformation studies have been adding another layer of information to gene expression for quite some time now, and the ubiquitous accessibility to short-read sequencing and new proximity ligation kits have been essential to move the field forward. Traditionally, restriction enzyme (RE) based approaches were used to determine chromatin conformation, but this comes with an intrinsic bias towards RE motifs instead of biological features. In this session you will learn about RE-independent approaches to proximity ligation and the added benefits to the resulting dataset: Omni-C: A Hi-C DNase, adding WGS capabilities to Hi-C for SNP calling and phasing. Micro-C: chromatin conformation with nucleosome-level resolution HiChIP MNase: combining Micro-C and ChIP-Seq for protein-directed chromatin architecture. Hybrid capture Hi-C pan promoter panel: studying gene regulation, developmental biology and complex trait mapping. Simple and effective means to probe known - and discover unknown - regulatory elements with a much lower sequencing burden. For more details: https://dovetailgenomics.com/webinar_expanding-hic-toolbox/.



Germline RNAs in the control of male fertility and epigenetic inheritance of diet-induced metabolic conditions.

Noora Kotaja, University of Turku, Finland

Abstract

Differentiating male germ cells, particularly meiotic spermatocytes and postmeiotic haploid round spermatids, have exceptionally diverse transcriptomes. After pervasive transcription in these cells, transcription is silenced due to chromatin compaction, and translational regulation becomes prominent when transcripts need to be translationally repressed and stored for later use. Some germline intrinsic RNAs are retained in transcriptionally inactive mature spermatozoa, and sperm RNA content is still modified during epididymal transit. These dynamic changes in the germline transcriptome require accurate regulatory mechanisms to monitor the quality of transcripts and determine their fates. This is critical for not only normal spermatogenesis and fertility, but also transmission of epigenetic information about father's environmental exposures and health condition to offspring via sperm RNAs. Our studies focus on elucidating the germline-specific RNA regulatory mechanisms, particularly the functions of cytoplasmic germ granules. Furthermore, we are interested in understanding the transgenerational effects of environmental exposures on germline transcriptome.



SPEAKERS

Small RNAs transmit big epigenetic message: Intergenerational reprogramming of metabolism.

Anita Öst, Linköping University, Sweden

Abstract

In parallel to the ongoing obesity epidemic, evidence that paternal nutrition at the time of conception modulates offspring's metabolic health, is rapidly accumulating. Because small RNAs have well-documented roles in gene regulation and epigenetics, they are prime candidates for transmitting environmental information across generations. To investigate the responsiveness of the human sperm small RNA repertoire, we fed healthy volunteers a high-sugar diet for one week. High-throughput smallRNA sequencing of sperm RNA followed up with extensive bioinformatic analysis revealed that high-sugar feeding shifts the abundance of both nuclear and mitochondrial tRNA fragments (tRF's). Similar experiments in *Drosophila* also showed a dynamic response of sperm tRF's in response to dietary shifts, especially the mitochondrial derived ones. Moreover, proteomic data reveal that there is a parallel rapid shift of a subset of proteins involved in metabolism and redox homeostasis. In line with this, we find that a short diet intervention is reflected in sperm mitochondrial ROS production. Thus, our data points to a model where mitochondrial dynamics is central in the rapid molecular changes in sperm in response to diet and suggest sperm mitochondria as a potential transmitter of diet/environment information across generations.



Transgenerational disruption of DNA methylation marks by ancestral folate supplementation is associated with enhanced axonal regeneration.

Bermans Iskandar, University of Wisconsin, USA

Abstract

The central nervous system (CNS) has limited ability to heal and regenerate after injury. Folate is crucial in enhancing axonal regeneration in CNS systems after sharp injury. We have shown that folate-induced axonal regeneration and DNA methylation in the spinal cord following sharp injury is dose-dependent and persists through 4 generations of untreated progeny, thereby demonstrating transgenerational epigenetic inheritance of a beneficial trait. Accordingly, we hypothesized that DNA methylation accounts for inheritance of the axonal regeneration phenotype. Whole genome bisulfite sequencing and enrichment to investigate 5-hydroxymethylation were conducted on injured spinal cord tissue from adult F3 male rats derived from an F0 lineage exposed to daily injections of folic acid vs. a vehicle control. We observed 1,635 and 624 folate-related differential methylation at CpG and CpH loci, respectively, and 657 folate-related differentially hydroxymethylated regions. Gene pathway analysis disclosed enrichment of differentially methylated and hydroxymethylated genes related to axonal and neuronal processes. Subsequently, we generated lineages in which only females or only males were treated with folic acid. We observed reduced regeneration in the F3 generation from F0 female-only and F0 male-only treated lineages compared to the F3 generation from lineages in which both the F0 female and male progenitors were treated with folic acid, with no significant difference between the gender-specific lineages. These data indicate that folate supplementation supports transgenerational inheritance of altered patterns of DNA methylation and hydroxymethylation associated with enhanced axonal regeneration of injured spinal cord axons. Inheritance is equivalently and additively transmitted via both sexes.



SPEAKERS

Circulating extracellular vesicles are vectors of communication with the germline that play a role in epigenetic inheritance

Anara Alshanbayeva, University of Zürich and ETH Zürich

Abstract

Environmental exposures can modify information in the germline by acting directly on germ cells or indirectly via somatic cells in gonads. In recent years, the possibility that soma-to-germline communication contributes to intergenerational inheritance has been suggested by studies in rodent models. But how signals in the periphery can reach germ cells in gonads is still not well understood. Blood has emerged as a potential vector of communication because it is a biological fluid that can capture physiological changes in the body and bring biological components across tissues. Our recent work showed that serum from adult male mice exposed to postnatal stress, injected chronically to naïve males can induce metabolic symptoms associated with stress in the offspring of the injected males (van Steenwyk et al EMBO J 2020). Building on this initial evidence, we conducted high-throughput proteomic, metabolomic and transcriptomic analyses of blood from exposed males to determine the components implicated in the transfer of information to sperm cells. We identified circulating extracellular vesicles as vectors of communication with germ cells that can reproduce symptoms of exposure in the offspring when injected to fathers in vivo. These results highlight the importance of circulating factors in the mechanisms of epigenetic inheritance.



The role of the epididymis in linking paternal exposures to alteration of the sperm epigenome (Talk recorded).

Brett Nixon, University of Newcastle, Australia

Abstract

Paternal exposure to environmental stressors elicits distinct changes to the sperm small noncoding RNA (sncRNA) profile; modifications that can have significant post-fertilization consequences. Despite this knowledge, there remains limited mechanistic understanding of how paternal exposures modify the sperm sncRNA landscape. To address this question, here we have exploited a tractable exposure model in which male mice were subjected to acute administration of the reproductive toxicant, acrylamide; a challenge that elicited robust changes to their sperm sncRNA profile. Further, we traced the differential accumulation of acrylamide-responsive sncRNAs to coincide with sperm transit of the proximal (caput) segment of the epididymis, wherein acrylamide exposure altered the expression of several transcription factors implicated in the expression of acrylamide-sensitive sncRNAs. We have also identified extracellular vesicles (epididymosomes) secreted from the caput epididymal epithelium in relaying altered sncRNA profiles to maturing spermatozoa, the implications of which manifest in the form of dysregulated gene expression during early embryonic development following fertilization by acrylamide-exposed sperm. Overall, these data provide mechanistic links to account for how environmental insults can alter the sperm epigenome and compromise the transcriptomic profile of early embryos.



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Isabelle Mansuy, UZH/ETH Zurich

Editing and Layout

Martin Roszkowski, UZH/ETH Zurich

Maria Dimitriu, UZH/ETH Zurich

Online Support

Lukas Hartmann, OnStage



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