Societat Catalana de BIOLOGIA

VI Jornada de Cromatina i Epigenètica

Organitzada per la Secció de Biologia Molecular de la Societat Catalana de Biologia (SCB)

amb el Barcelona Chromatin Club (BCC)

INSTITUT D´ESTUDIS CATALANS

Carrer del Carme, 47

Barcelona

8 de març de 2016

VI Annual Chromatin and Epigenetics symposium

Organized by the Molecular Biology section of the Catalan Society of Biology (SCB)
—Albert Jordan—

and the Barcelona Chromatin Club (BCC)
—Sonia Forcales—

March 8, 2016

IEC: carrer del Carme, 47, Barcelona

Prat de La Riba hall

Sponsored by:

Institut d'Estudis Catalans

Covalab

Active Motif

PROGRAM

8.20-8.50 ***Registration and documentation pickup***

8:50 ***Opening***

Session I. *Chair:* María José Barrero (CNIO)

9.00-9.20 **15min+5**
Sandra Peiró (IMIM)
Chromatin condensation protects breast cancer cells from the DNA damage repair machinery

9.20-9.40 **15min +5**
Josep Jiménez (Htal. St Joan de Déu)
Nongenomic inheritance of diabetes risk through the paternal line. Exploring DNA methylation in spermatozoa

9.40-9.50 Short talk **7min +3**
Malte Beringer (CRG)
C17orf96 protein bridges polycomb and elongin BC to functionally link them in embryonic stem cells

9.50 -10:00 Short talk **7min +3**
Juergen Walther (IRB)
Towards multiscale investigation of base-pair level properties of chromatin

10.00-10:10 Short talk **7min +3**
Jordi Moreno (Swedish University of Agricultural Sciences)
Parental epigenetic asymmetry in the Arabidopsis endosperm

10.10-10:30 **15min +5**
Albert Jordan (IBMB-CSIC)
Specificities on the genomic distribution of human histone H1 subtypes

10:30-10:40 **10 x 1min**
Speed poster presentations

10:40-11.20 ***Coffee break and poster session sponsored by Covalab***

Session II. *Chair:* Miguel Angel Peinado (IMPPC)

11.20-11.40 **15min +5**
Jorge Ferrer (IDIBAPS, Imperial College London)
Noncoding genome function in pancreatic beta cells

11.40-12.00 **15min +5**
Sara Pagans (IDIBGI-Univ. Girona)
Getting to the heart of arrhythmogenic diseases: Role of transcriptional dysregulation

12.00-12.20 **15min +5**
Inma Hernández (IMIM)
RING1B contributes to Ewing sarcoma development by repressing the NaV1.6 sodium channel and the NF-kB pathway, independently of the fusion oncoprotein

12.20-12.30 Short talk **7min +3**
Montserrat Barragán (Clínica Eugin)
Effect of vitrification and warming on imprinted genes and DNA methyltransferases expression in MII oocytes from young fertile women

12.30-12.40 Short talk **7min +3**
Sílvia Pérez (CRG)
Transcription without canonical histone marks

12.40-12.50 Short talk **7min +3**
Elena Gómez (Estación Biológica Doñana-CSIC)
Epigenetic regulation of Plasmodium falciparum development and adaptation in the mosquito

12.50-13.10 **15min +5**
Manel Esteller (PEBC-IDIBELL)
Cancer Epigenetics: From Knowledge to Applications

13.20-15:00 Lunch

Session III-BCC. Epigenetic reprogramming

Chair: Bernhard Payer (CRG)

15.00-15.10 Sponsor' talk **7min +3**
Sarantis Chlamydas (Active Motif)
Advances in Chromatin Immunoprecipitation

15.10-15.40 **25min +5**
Alvaro Rada-Iglesias (University of Cologne)
Epigenomic-based identification of spinal neural tube patterning regulators

15.40-16.00 **15min +5**
Sonia Forcales (IMPPC-IGTP)
Epigenetic reprogramming of a pericentromeric repeat in colorectal cancer

16.00-16.20 **15min +5**
Pierre-Antoine Defossez (CNRS, Paris)
A histone mimic within DNA Ligase 1 recruits UHRF1 to sites of DNA replication: implications for DNA remethylation

16.20-16.40 **15min +5**
Laia Richart (CNIO)
The chromatin remodeller BPTF acts as a barrier during somatic cell reprogramming

16:40-17.20 Coffee break and poster session sponsored by Active motif

Session IV. *Chair:* Guillaume Filion (CRG)

17:20-17.40 **15min +5**
Ferran Azorin (IBMB-CSIC, IRB)
HP1 proteins in transcription regulation and maintenance of genome stability

17.40-18.00 **15min +5**
Rafael Oliva (IDIBAPS, UB)
Sperm cell proteome and epigenetics

18.00-18.10 Short talk **7min +3**
Farners Amargant (CRG, Clínica Eugin)
Characterization of the human sperm centrosome and its role in fertility

18.10-18.20 Short talk **7min +3**
Dafni Anastasiadi (ICM-CSIC)
Natural patterns of DNA methylation and gene expression in fish

18.20-18.40 **15min +5**
Dave Monk (PEBC-IDIBELL)
Human germline methylation: Selected survival of imprints

18.40 Meet together for a beer

Secretaries of SCB:

Mariàngels Gallego and Maite Sánchez
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Coorganized by:

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Institut de Medicina Predictiva i Personalitzada del Càncer (IMPPC)
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Posters:

1.Roberto Malinverni (JCLRI)
regioneR: an R package for the management and comparison of genomic regions

2.Ferran Barrachina (IDIBAPS)
Patients with impaired spermatogenesis have a deregulated Histone H4 hyperacetylation pattern

3.Dolors Puigoriol (UB)
Environmental enrichment modified epigenetic mechanisms in SAMP8 reducing oxidative stress and inflammaging and achieving neuroprotection

4.Sarah Hurtado (JCLRI)
A splicing switch of the histone variant macroH2A1 couples the chromatin state to energy metabolism

5.Vahan Serobyan (Max Planck Institute for Developmental Biology)
A genetic locus with dual-coding transcripts generates a short open reading frame required for phenotypic plasticity in nematodes.

6.Diana Buitrago (IRB)
Deciphering correlations between DNA methylation, nucleosome positioning and gene expression

7.Izaskun Mallona (IMPPC/IGTP)
Mining the DNA synmethylome to explore genomic regulation in human cancer

8.Marta Sánchez (PEBC-IDIBELL)
Absence of maternal methylation in biparental hydatidiform moles with NLRP7 maternal-effect mutations reveals widespread placenta-specific imprinting

9.Keyvan Torabi (UAB)
Transcription-dependent radial distribution of genes in chromosome territories

10.Raquel Fueyo (IBMB-CSIC)
TGFß controls the establishment of neural enhancers by coordinating the action of histone modifying enzymes and chromatin remodelers

C17orf96 Protein Bridges Polycomb and Elongin BC to Functionally Link Them in Embryonic Stem Cells

Malte Beringer,[1,4] Paola Pisano,[2,4] Valerio Di Carlo,[1,4] Enrique Blanco,[1] Michael Wierer,[2] Paul Chammas,[1] Pedro Vizán,[1] Arantxa Gutiérrez,[1] Sergi Aranda,[1] Bernhard Payer,[1] and Luciano Di Croce[1,3]

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The chromatin of stem cells displays factors of both repressive and activating function at the same genomic sites, for example at histone-modified bivalent regions. At these targets, the histone-modifying Polycomb repressive complex 2 (PRC2) is required to maintain the transcriptionally repressed state; however, repression is not complete. Here, we have elucidated that the PRC2-associated protein C17orf96, which is expressed in the inner cell mass of the mouse epiblast, functions as a BC box protein to bring the transcription elongation factors Elongin BC to PRC2-repressed genomic targets. Both C17orf96 and Elongin BC are required to maintain low levels of expression, a characteristic feature of PRC2-repressed sites. Balancing activating and repressive cues is therefore a more general feature of bivalent regions in stem cells than previously appreciated.

Towards multiscale investigation of base-pair level properties of chromatin

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The three dimensional organization of chromatin inside the cell nucleus is expected to strongly depend on sequence specific properties of nucleosomal and linker DNA. However, recent experiments [1] cannot capture yet the characteristics of chromatin arrangement on the resolution level of a single base-pair. To model the chromatin fiber with bp-level accuracy we first developed a coarse-grained DNA model (CG) to investigate sequence dependent DNA properties (simulation times ~10^5 times faster than conventional all atom molecular dynamics (MD) simulations). In our model, DNA is represented intrinsically at base pair level with an elastic potential representing the interactions between adjacent base pairs. Coupling terms between base pairs are extracted from atomistic MD simulations with the improved parmbsc1 force field [2]. A comparison of DNA structures generated by CG and by all atom MD reveals striking similarity of important features such as distribution of helical parameters and bending. To extend the DNA model towards chromatin, firstly linker DNA is sampled as described above and secondly nucleosomal DNA is introduced as rigid DNA in between the linkers. Electrostatic and steric potentials account for long-range intra-fiber interactions. This makes it possible to study the characteristics of kbp-long chromatin fibers of arbitrary sequence at base pair level accuracy.

Parental Epigenetic Asymmetry in the Arabidopsis Endosperm

Jordi Moreno-Romero, Juan Santos-González, Claudia Köhler

Department of Plant Biology, Uppsala BioCenter, Swedish University of Agricultural Sciences and Linnean Center of Plant Biology, Uppsala, Sweden

The plant endosperm is an ephemeral tissue required to support embryo growth, similar to the nourishing role of the placenta. Like the mammalian placenta, the endosperm is a battleground for parental conflict, reflected by the expression of parent-of-origin expressed imprinted genes. Imprinted genes are marked by parental-specific epigenetic marks that are established in the gametes and maintained in the endosperm after fertilization by unknown mechanisms.
Using maternal and paternal sequence polymorphisms we were able to differentiate the parental origin of histone modifications and DNA methylation in the early endosperm and to investigate the interplay among the different marks. Our study reveals that Polycomb-mediated H3 lysine 27 trimethylation (H3K27me3) is preferentially localized to DNA hypomethylated regions that are targeted by the DNA glycosylase DEMETER, linking DNA demethylation and H3K27me3 to imprinted gene expression. We furthermore show that H3K27me3 marked regions are located at centromeric and pericentromeric regions, unlike the euchromatic localization of this mark in vegetative tissues, suggesting a silencing role of Polycomb group proteins for heterochromatic regions in the endosperm.

Effect of vitrification and warming on imprinted genes and DNA methyltransferases expression in MII oocytes from young fertile women

Montserrat Barragán, Aïda Pujol, Albert Obradors, Valérie Vernaeve, Rita Vassena.

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Relevance/Impact: Epigenetic modifications such as DNA methylation are conserved through evolution and play important roles in development. Animal data shows that loss of imprinting and DNA methylation are associated with ART procedures. However, human studies are often hampered by the fact that available oocytes almost invariably come from infertility affected patients, thus making it hard to dissect the source of epigenetic alterations caused by ART from those caused by genetic predisposition.

Aims/Objective: The aim of the present study was to investigate the effect of vitrification-warming of MII human oocytes on the expression of genes in the imprinting network.

Contents: This study includes 42 MII oocytes matured *in vivo* from 26 healthy and fertile donors <35 years of age, after controlled ovarian stimulation (rFSH) with GnRHa as hypophysis down-regulator and GnRH agonist as maturation trigger. Oocytes were either analyzed fresh (n=26) or after open vitrification/warming (Cryotop, n=16).
Total RNA was isolated from samples of 1 or 2 oocytes each using TRIZOL; cDNA synthesis was performed by random hexamers priming using Cloned AMV kit. In each oocytes, we investigated the expression of the genes: IGF2R, SNRPN, DNMT1, DNMT3a, DNMT3b, and DNMT3L. Differences were analyzed by Student's t-test.

Outcomes: Vitrification-warming significantly decreased the mRNA amount of *DNMT1* and *DNMT3a* ($p<0.001$ and $p=0.001$; respectively); no significant differences were found for *DNMT3b* and *DNMT3L* expression. Significant decreased expression of *IGF2R* was also detected after vitrification-warming ($p=0.002$), but not of *SNRPN*.

Discussion: We found a significant effect of vitrification-warming on the expression of genes related to the epigenetic state of the MII oocyte. Importantly, our data are based on oocytes from young fertile donors, thus the observed result should be due to the ART technique, rather than a predisposed (infertile or aged) background. Further studies are needed to define the clinical relevance of our findings.

Epigenetic regulation of Plasmodium falciparum clonally variant gene expression during its sporogonic development in the mosquito

Elena Gómez-Díaz1,4, Rakiswendé S. Yerbanga2, Thierry Lefèvre2,3, Anna Cohuet2,3, Jean Bosco Ouedraogo2, and Victor G. Corces1

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SUMMARY
P. falciparum phenotypic plasticity is linked to the variant expression of clonal multigene families such as the var genes. We have examined changes in transcription and histones modifications that occur during sporogonic development of P. Falciparum in the mosquito host. In general, the active or inactive transcriptional state of a gene correlates with the presence of active or repressive histone modifications, respectively. However, a number of developmentally regulated genes are expressed during the sporozoite stage in spite of the presence of H3K9me3, and these include clonally variant genes. All var genes are silenced in the gametocyte blood stages of the parasite in the human host. After infection of mosquitoes, a single var gene is selected for expression in the oocyst, while the rest remain silenced, and transcription of this gene increases dramatically in the sporozoite. Interestingly, the same PF3D7_1255200 var gene was activated in 4 different experimental infections. Transcription of this var gene during parasite development in the mosquito correlates with the presence of low levels of H3K9me3 at the binding site for the PF14_0633 AP2 transcription factor. This chromatin state in the sporozoite also correlates with the expression of an antisense long non-coding RNA (lncRNA) that has previously been shown to promote var gene transcription in erythrocytes. Expression of both the sense protein-coding transcript and the antisense lncRNA increase dramatically in sporozoites. The findings suggest a
complex process for the activation of a single particular var gene that involves AP2 transcription factors and expression of an antisense lncRNA.

Advances in Chromatin Immunoprecipitation

Sarantis Chlamydas, Carlos Baptista, Bryce Alves, Adam Blattler, Maddy Craske Chisato Henry, Mary Anne Jelinek, Paul Labhart, , Garrett Shafer, Brian Egan, Terry Kelly
Active Motif Inc, Carlsbad, Ca.

Chromatin Immunoprecipitation or ChIP has provided many important insights into a variety of biological processes and diseases. However as we ask more complex questions the limitations of traditional ChIP have impeded our scientific advancements. Active Motif has developed a variety of tools and services to overcome many of these challenges, including normalizing across samples, performing ChIP on targets for which ChIP grade antibodies are not available, increasing resolution and identifying binding partners.

Many global differences in histone modification levels cannot be seen when performing ChIP-Seq due to sample and condition variations. To resolve this problem, we have developed a Spike-In strategy specifically for ChIP, which not only normalizes for biological variation across samples but also for technical variation that can occur during the ChIP procedure.

In order to overcome , the lack of availability of a ChIP-grade antibody, we have designed a tag specifically for ChIP (AM-tag, Patent Pending). AM Tag is consist of a small, unstructured sequence that can be attached to any protein of interest and successfully used in ChIP-Seq.

DNA binding proteins typically form complexes when binding to chromatin and the subunits of a given complex can impact which genomic regions are bound.. To identify potential chromatin protein complexes, Active Motif has commercialized RIME (Rapid Immunoprecipitation Mass spectrometry of Endogenous proteins) developed by Dr. Jason Carroll. This protocol enables the unbiased Mass Spec based detection of chromatin based protein-protein interactions.

Specific locus,ChIP (enChIP), enables studies between promoter and enhancers and allows the study of chromosomal conformation and genomic structure. Using the dCas9 technology for genome editing we are able to target specific locus and analyze by ChIP seq experiment the interactome under different conditions.

These tools along with a variety of other epigenetic related assays and services developed by Active Motif enable scientists to answer a variety of biological questions in unprecedented detail.

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Epigenetic reprogramming of a pericentromeric repeat in colorectal cancer

Gabrijela Dumbovic[1], Jordi Banús[1], Cristian Polo[1], Josep Biayna[1] Johanna K. Samuelsson[2], Sergio Alonso[1], Sonia Forcales[1] and Manuel Perucho[1]

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Our study shows that hypomethylation of a pericentromeric tandem repeat, SST1, occurs in approximately 22% of colorectal cancers (CRC). High SST1 demethylated cases associate with p53 mutations and are age-independent, which suggests that other causes than age-deregulated methylation mechanisms may contribute to SST1 demethylation in colorectal cancer. HELLS, an helicase described as an epigenetic guardian of repetitive elements is involved in maintaining SST1 elements methylated.

SST1 demethylation correlates with changes in histone post-translational modifications and with increased SST1 transcription in primary samples and in several cancer cell lines. Importantly, in CRC cells with highly methylated SST1, treatments with AZA and especially with AZA/TSA, increase SST1 expression levels comparable to housekeeping genes. Characterization of the SST1 transcript shows it is non-polyA, transcribed by polymerase II and associated to the insoluble nuclear fraction, which is a characteristic of non-coding RNAs. Intriguingly, Northern blot analysis revealed three SST1 main transcripts originated from specific chromosomes. To understand the relevance SST1 ncRNA may have in CRC disease, RNA-affinity purification analyses combined with downregulation approaches are underway.

Somatic DNA demethylation especially at repetitive elements has been linked to genomic instability although the mechanisms linking these events are not fully understood. Whether SST1 RNA may contribute to connect these events is under investigation.

A histone mimic within DNA Ligase 1 recruits UHRF1 to sites of DNA replication: implications for DNA remethylation

Alexandra Fournier1, Laure Ferry1, Takeshi Tsusaka2, Tadahiro Shimazu2,
Kyohei Arita3, Yoichi Shinkai2, Pierre-Antoine Defossez1

1: CNRS, Paris, France; 2:RIKEN, Wako, Japan; Yokohama City University, Japan.

DNA methylation is an essential epigenetic mark in mammals: it controls the expression of imprinted genes, germline genes, transposons, and is intimately linked to the local chromatin state.For all these reasons, the maintenance of correct patterns of DNA methylation is essential for the survival of mammalian cells. This pattern has to be re-established at each round of DNA replication. One of the key actors in this process is the protein UHRF1: it is essential for DNA remethylation after replication, but its mode of action is unclear. We have characterized the UHRF1 interactome by proteomics and found that DNA Ligase 1 (LIG1) is a highly abundant interactor of UHRF1. We have mapped the interaction domains and found that a Tudor domain of UHRF1 interacts with an H3-like histone mimic within LIG1. We show that the interaction requires the methylation of the LIG1 histone mimic by the lysine methyltransferases G9a or GLP.Finally, we find that the interaction with LIG1 promotes the recruitment of UHRF1 to sites of DNA replication. These results prompt a reinterpretation of the function of UHRF1's Tudor domain, which we show can bind non-histone proteins. They also reveal a new level of complexity in DNA Ligase 1, identify a new non-histone target of G9a and GLP, and provide the first example of a histone mimic that coordinates DNA replication and DNA remethylation.

The chromatin remodeller BPTF acts as a barrier during somatic cell reprogramming

Applicant: Laia Richart Ginés
Group: Epithelial Carcinogenesis
Institution: Spanish National Cancer Research Centre (CNIO)

Transduction of the transcription factors OCT3/4, SOX2, KLF4, and c-MYC (OSKM) into a wide variety of cell types initiates a reprogramming process that converts them into embryonic stem (ES)-like cells designated induced pluripotent stem cells (iPSCs). This process requires a profound epigenetic remodelling, including early changes in histone modifications, DNA demethylation, and reactivation of the inactivated X chromosome at later stages. Therefore, chromatin-modifying and -remodelling complexes can act as barriers or facilitators of reprogramming.

Among these factors, c-MYC is not absolutely required for reprogramming of somatic cells (i.e. mouse embryonic fibroblasts), although it dramatically enhances the efficiency and kinetics of the process. c-MYC is thought to facilitate the initial steps, both by repressing fibroblast-specific genes and by enhancing the binding of OSK to chromatin. In addition, c-MYC regulates DNA replication and global histone acetylation, which may facilitate the reprogramming process more indirectly.

We have recently described that c-MYC interacts with BPTF, the largest and essential subunit of the ATP-dependent chromatin remodeller NURF (Nucleosome Remodelling Factor). BPTF provides specificity to NURF through its interaction with both transcription factors and histone modifications (H3K4me3 and H4K16ac). We showed that BPTF silencing impairs the activation of the full c-MYC transcriptional program and is associated with decreased c-MYC recruitment to promoters and a reduction in DNA accessibility at c-MYC target chromatin. To evaluate the biological relevance of the c-MYC:BPTF interaction, we have tested c-MYC ability to cooperate with OSK in the reprogramming of wild type or *Bptf*-null mouse embryonic fibroblasts (MEFs). Genetic inactivation of BPTF did not impair cell proliferation but had a profound impact on the efficiency of iPSC generation, affecting the kinetics of reprogramming and reducing the number of emerging iPSC colonies. Similar observations were made when c-MYC was removed from the reprogramming cocktail, indicating that BPTF is critical for iPSC reprogramming in a manner that is not contingent on exogenous c-MYC.

Therefore, we propose that the chromatin remodeller BPTF acts as a facilitator of reprogramming. The mechanisms involved therein are not yet understood, but we hypothesize that BPTF promotes reprogramming by enhancing the transcriptional activation of silenced loci by the OSK factors

Characterization of the human sperm centrosome and its role in fertility

Farners Amargant[1,2], Montserrat Barragán[2], Sylvain Meunier[1], Rita Vassena[2], Isabelle Vernos[1,3]
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During fertilization, beside a haploid genome, the sperm provides the mature oocyte with a centrosome. The male centrosome assists in the fusion of the pronuclei and in the establishment of the axis of embryonic cell divisions. The objective of this study was to test the functionality of the human sperm nuclei and their associated centrosomes to nucleate microtubules in an *ex vivo* xenogeneic system using *Xenopus laevis* egg extract (EE).
Xenopus frogs were stimulated with 100 and 1.000 I.U of PMSG and HCG respectively to lay eggs arrested in MII. The eggs were centrifuged at 17.000g at 4ºC; 3.000 sperm nuclei were demembranated in Triton X-100 + DTT and incubated in EE at 20ºC during 150min. The structures obtained were classified in: bipolar spindles (BP), abnormal nucleation (AB - nucleate microtubules but do not generate a spindle), and no nucleation (NN). Each sample was incubated four times in different EE and 200 sperm nuclei per condition and incubation were analyzed.
We found that 64±2,6% of human normozoospermic sperm nuclei (n=9) form BP; 21±2,6% form AB and 15±2,5% NN. Furthermore, the contribution of the centrosome was validated by immunofluorescence, proving that centrosomes localize to the spindle poles. Moreover, isolated centrosomes, stripped from their centriolar material, incubated in EE and pure tubulin could nucleate microtubules, confirming that human centrosomes are nucleators in EE. Furthermore, sperm samples with different diagnosis were able to nucleate microtubules similarly: astenozoospermic BP=60±1,1%, AB=29±3,6%, NN=12±2,7%, n=3; teratozoospermic BP=65±5,3%, AB=28±5,9%, NN=7±4,1%, n=1; oligoteratozoospermic BP=56±6,6%, AB=32±4,2%, NN=12±7,2%, n=1, suggesting that the chromosomal pathway of microtubule nucleation can compensate possible defects in the centrosomal activity. In conclusion, we established a novel and potent model to study the centrosomal and chromosomal-regulated processes that occur during human fertilization. Moreover, we demonstrate that human centrosomes, isolated from sperm cells, are active nucleators in EE.

Human germline methylation: Selected survival of imprints

Marta-Sanchez-Delgado[1], Ana Monteagudo-Sanchez[1], Alex Martin-Trujillo[1], Enrique Vidal[2], Franck Court[3], Carlos Simon[4], David Monk[1].

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It has recently been shown that the gametes from both mouse and humans show largely opposing methylation profiles with only ~45% of the methylomes of sperm and oocytes exhibiting comparable patterns. Within a few hours of fertilization a wave of global epigenetic reprogramming ensures that methylation in the blastocysts are at their lowest levels, erasing the majority of this gamatic epigenetic information. However some specific sequences survive this demethylation, specifically those located with imprinted regions and certain repeat subtypes. Imprinted genes are only transcribed from one parental allele leading to parent-of-origin specific expression, with allelic expression directly controlled by allelic methylation. Here we present the data describing the fate of germline-derived methylation in humans. With the exception of a few known paternally methylated gDMRs associated with known imprinted domains, we demonstrate that sperm-derived methylation is reprogrammed by the blastocyst stage of development. In contrast a large number of oocyte-derived methylation difference survive to the blastocyst stage, but uniquely persist as maternally methylated DMRs only in the placenta. Furthermore, we demonstrate that this phenomenon is exclusive to humans and primates, since no placenta-specific maternal methylation was observed in mouse, horse, cow and dog. Utilizing single cell RNA-seq datasets from human pre-implantation embryos we show that following embryonic genome activation the maternally methylated tDMRs orchestrate imprinted expression. However, despite showing imprinted expression of 28 genes, transcriptional profiling revealed that not all placenta-specific maternally methylated DMRs coordinate imprinted expression, suggesting differential reading of this epigenetic mark during human development.

RegioneR: an R/Bioconductor package for the association analysis of genomic regions based on permutation tests

Bernat Gel[1†], Anna Díez-Villanueva[1†], Eduard Serra[1], Marcus Buschbeck[1,2], Miguel A. Peinado[1] & Roberto Malinverni[1,2*]

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[2]Josep Carreras Institute for Leukaemia Research (IJC), Campus ICO-HGTP, Campus Can Ruti, Badalona, Spain

[†] Equally contributed

Statistically assessing the relation between a set of genomic regions and other genomic features is a common challenging task in genomic and epigenomic analyses. Randomization based approaches implicitly take into account the complexity of the genome without the need of assuming an underlying statistical model. regioneR is an R package that implements a permutation test framework specifically designed to work with genomic regions. In addition to the predefined randomization and evaluation strategies, regioneR is fully customizable allowing the use of custom strategies to adapt it to specific questions. Finally, it also implements a novel function to evaluate the local specificity of the detected association. RegioneR is an R package released under Artistic-2.0 License. The source code and documents are freely available through Bioconductor (http://www.bioconductor.org/packages/regioneR).

Patients with impaired spermatogenesis have a deregulated Histone H4 hyperacetylation pattern

Ferran Barrachina[1], Carme Mallofré[2], Orleigh Addelecia Bogle[1], Afsaneh Goudarzi[3], Ada Soler-Ventura[1], Anat Melnick[4], Juan Manuel Corral[4], Sophie Rousseaux[3], José Luís Ballescà[5], Rafael Oliva[1]

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Spermatogenesis is a differentiation process characterized by extremely marked chromatin and cellular changes leading to the highly specialized sperm cell. It is well known that histone H4 hyperacetylation (acH4) during spermatogenesis is involved in gene activation and in sperm chromatin remodelling in the final stages, and therefore may affect the imprinting of the mature sperm cell. Thus, we hypothesized that acH4 expression pattern during spermatogenesis is different between normal and pathological samples. We used a semi-quantitative approach to compare both the intensity and distribution of acH4 immuno-detection in testicular biopsies (n=23) with normal and abnormal spermatogenesis (hypospermatogenesis, spermatogenic arrest and Sertoli cell-only Syndrome). Immunofluorescence was used to further localize acH4 in ejaculated sperm cells. AcH4 immuno-detection was high in spermatogonia, decreased in spermatocytes, and increased again reaching a maximum in elongating spermatids in normal spermatogenesis. The immuno-detection of acH4 in all spermatogenic cell types decreased in patients with hypospermatogenesis or spermatogenic arrest, but increased in the presence of tubular atrophy and fibrosis. Stronger acH4 immuno-detection was observed in Sertoli cells from patients with Sertoli cell-only Syndrome (absence of germinal cells). The localization of acH4 in the mature sperm nucleus indicates the acetylation of retained H4 histones. In conclusion, we found that acH4 is deregulated in patients with altered spermatogenesis. The results from this study implicate acH4 involvement in the remodelling of chromatin during the histone-to-protamine transition through spermatogenesis which may play a role in chromatin imprinting anomalies. Supported by EU-FP7-PEOPLE-2011-ITN-289880, Ministerio de Economia y Competividad PI13/00699, Fundación Salud 2000 13-015 and EUGIN-UB to RO.

Environmental enrichment modified epigenetic mechanisms in SAMP8 reducing oxidative stress and inflammaging and achieving neuroprotection

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With the increasing of life expectancy, ageing and age-related cognitive impairments are becoming one of the most important issues for human health. At the same time, it has been shown that epigenetic marks are emerging as important factors of the overall in life expectancy. In fact, epigenetic is responsible of the establish the specific expression programs and interacts with environmental and stochastic factors.

Therefore, understanding the epigenetic modifications by which environmental enrichment (EE) interacts in the brain and affect learning and memory, novel therapeutics can be developed to neurodegenerative diseases and aging.

For this reason, we focus to demonstrate that environmental enrichment (EE) mitigates epigenetic modification produced by aging, well as produces reducing brain senescence hallmarks in SAMP8 at 4 months of age. The SAMP8 were established via phenotypic selection of the AKR/J mouse strain and exhibits age-related deterioration in learning and memory abilities and is useful as a model of neurodegenerative disease.

We found that EE increases DNA-methylation levels (5-mC) and reduces hydroxymethylation levels (5-hmC) as well as reduces histone acetylation levels. Likewise, we found changes in the hippocampal gene expression of some chromating modifying enzymes like *Dnmt3b, Hdac1, Hdac2, Sirt2 and Sirt6* and all of this epigenetic context correlate with increased expression of antioxidants genes such as *Hmox1, Aox1, Cox2* and reduced expression of inflammatory genes as *Il-6, Cxcl10* and achieve neuroprotection and cognitive improvement.

In conclusion, EE can be a feasible intervention for understand more concretely what are the most important epigenetic keys in the process of neurodegeneration and memory loss.

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A genetic locus with dual-coding transcripts generates a short open reading frame required for phenotypic plasticity in nematodes

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Short open reading frames (sORF) are often found within or overlapping with major transcripts. However, little is known about their coding potentials and functions. Here we characterize a complex mutation in the *eud-2* gene in the nematode *Pristionchus pacificus* that has a pleiotrpic defects including sex determination and mouth-form development. We show that *eud-2* has dual coding transcripts with *eud-2a* encoding a chromodomain protein *and eud-2b*, which covers 5' UTR, the last intron and the last exon and the 3' UTR of *eud-2a* encoding a sORF. Characterization of the original allele, transgenesis experiments and CRISPR/Cas9 induced deletion alleles show that the chromodomain transcript *eud-2a* regulates locomotion and sex determination. In contrast, *eud-2b* is translated into a peptide of 40 aminoacids and controls mouth-form plasticity. This small peptide is localized in the nucleus throughout development. Thus, our study provides evidence for the functional significance of sORF and strengthens the view that the regulation of developmental plasticity involves unusual molecular modules.

Deciphering correlations between DNA methylation, Nucleosome positioning and Gene expression

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DNA methylation has been studied extensively, different patterns have been associated to cancer, and some mutations in DNA methyltransferases (DNMTs) have been linked to certain diseases. However, the biological function of DNA methylation on regulation and chromatin structure has not been well established and the mechanisms that determine activity of DNMTs in vivo are unknown. Some studies have shown methylation linked to gene silencing, but methylation in gene bodies has been associated to active transcription. DNA methylation might affect gene expression through modification of chromatin structure, compacted in units called nucleosomes. Relation between nucleosomes and methylation has been studied but there is no consensus on how the two factors interact. Some studies claim that methylated DNA is less flexible and hence less likely to form nucleosomes. In contrast, other studies found that methylation occurs preferentially in nucleosomal DNA. Conflicting results might come from the large complexity of mammalian genomes and it would be helpful to study DNA methylation in a simpler organism.
In order to study the correlation between methylation, nucleosome occupancy and gene expression we have induced DNA methylation expressing four murine DNMTs in the natively unmethylated genome of Saccharomyces cerevisiae, which does not contain any protein or protein homologue related to DNA methylation or de-methylation. Our experiments show a well defined patter along the genome, with promoter regions having low levels of CpG methylation and increasing towards transcription termination sites. Nucleosome occupancy and methylation levels are negatively correlated and methylation is higher in promoters of repressed genes. We observed specificity of DNMT3b in a particular sequence context and DNMT1 was not performing methylation maintenance in absence of other proteins. Overall, our results show this model is valid to study several aspects of DNA methylation in vivo that can be masked by other mechanisms present in more complex organisms.

Mining the DNA synmethylome to explore genomic regulation in human cancer

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The analysis of DNA methylation can unveil epigenetic patterns that play a role in carcinogenesis. For instance, overall hypomethylation and local promoter hypermethylation are common phenotypes of tumor samples. However, beyond local effects of DNA methylation changes on the regulation of neighbouring genes, little is known on the impact of long range associations.

Here we report a new method to summarize the DNA methylation changes that occur in a coordinate manner. To calculate the associations, we propose the sequential computing of the pairwise correlations of more than 200 thousands CpGs, regardless of their genomic location, thus being able to detect long range phenomena.

We applied the method to two series of colon cancer samples independently, the Cancer Genome Atlas (TCGA) and the Colonomics datasets, as well to their matched normals. Modelling the result as a network, in which the CpGs are the edges and the links, the correlations, we detected new genomic compartments of highly connected CpGs that are associated to genetics, epigenetics and clinical features. We explored whether these communities, which we call synmethylation modules, are conserved in normal and tumors and across the Colonomics and TCGA datasets. We are developing a Web tool to facilitate the queries to the colon cancer DNA synmethylome.

Transcription-dependent radial distribution of genes in chromosome territories

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Human chromosomes occupy distinct territories in the interphase nucleus. Moreover, a nonrandom organization of chromosome territories (CTs) and genes within the nucleus has been proposed in the last decades. It is well-accepted that CTs are positioned in a radial distribution within the nucleus. Whereas gene-rich CTs are generally located in the center of the nucleus, gene-poor CTs are more prone to be located close to the nuclear periphery. Moreover, a non-random distribution for individual genes, where gene activity could be increased as we move towards the center of the nucleus, it is also found. On the other hand, a relationship between gene expression and location respect the CT itself is more discussed. Whereas some studies argue in favor of a more peripheral location of over-expressed genes within the CT, others did not find any correlation.

In the present study we performed 3D-FISH experiments in DLD1, a colorectal cancer cell line, using Whole Chromosome Paintings (WCP) for chromosomes 8 and 11 and labeled BAC clones covering four genes with different expression levels assessed by gene expression arrays and RT-PCR. Moreover we synchronized the cultures in order to assess nucleus in the same cell cycle phase. Our results confirmed that over-expressed genes, *MYC* in chromosome 8 and *CCND1* in chromosome 11, are located significantly more far away from the center of the CT compared to under-expressed genes of the same chromosome, *DLC1* and *SCN3B*, respectively. Thus, we suggest a nonrandom organization where over-expressed genes are located close to the periphery of the CTs in order to be easily transcribed compared to under-expressed genes.

TGFß controls the establishment of neural enhancers by coordinating the action of histone modifying enzymes and chromatin remodelers

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TGFß pathway is a context-dependent signaling cascade that through the activation of SMAD proteins dictates the transcriptional program that will operate in every cell environment. How this context-specificity is imprinted depends on the interactors of SMAD in that particular cellular type. In this work, we demonstrate that the transcriptional program regulated by TGFß in a neural stem cell model is determined by the presence of the helix-loop-helix master regulator ASCL1 on enhancers. Furthermore, we have analyzed the molecular mechanism that operates on these enhancers concluding that proper enhancer activation requires the combined action of the histone demethylase JMJD3 and chromatin remodelers together with members of the MLL family. This protein complex is recruited to neural enhancers and by methylating the H3K4 and synthesizing eRNA create the necessary chromatin structure for correct gene activation.

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