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Barcelona conference on epigenetics and cancer: 50 years of histone acetylation

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Abstract

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The Barcelona Conference on Epigenetics and Cancer (BCEC) was held in Barcelona, Spain, on October 1st and 2nd, 2014. The meeting was co-organized by the Cancer Epigenetics and Biology Program (PEBC-IDIBELL) and B·Debate, an initiative of Biocat, with the support of "la Caixa" Foundation. The scientific committee was comprised of leading scientists in the field of epigenetics: Dr. Manel Esteller, director of PEBC-IDIBELL, Dr. Alejandro Vaquero and Dr. Esteban Ballestar, from PEBC-IDIBELL, Juan Ausió from the University of Victoria (Canada), and Marcus Buschbeck, from the Institute of Predictive and Personalized Medicine of Cancer (IMPPC), as BCEC series coordinator. This meeting was the second edition of the BCEC series, which was launched by 5 leading Barcelonan institutes to bring together leading investigators in the fields of epigenetics and chromatin research. The topics discussed during the meeting included the current challenges, opportunities, and perspectives surrounding the study of histone modifications (focusing in acetylation), chromatin structure and gene expression, and the involvement of histone acetylation in physiology and diseases, such as cancer or neurological diseases.

Keywords: acetylation, cancer, epigenetics, histone

Welcome and Introduction

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Juan Ausió (University of Victoria, Victoria, Canada) welcomed participants and acknowledged the scientific committee and B·Debate organization. Dr. Ausió reminded the audience that this meeting was a celebration of the 50th anniversary of the publication of the paper “Acetylation and methylation of histones and their possible role in the regulation of RNA ” by V.G. Allfrey, R. Faulkner, and A. E. Mirsky, which was published in PNAS in 1964.[1] The paper was seminal in establishing the relationship between histone post-translational modifications (PTMs) and gene expression, and opened up an important new field in epigenetic research.

Histone Acetylation: General Concepts

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Bryan Turner (University of Birmingham, Birmingham, UK) opened the session by outlining the advantages conferred to eukaryotes over prokaryotes by the presence of the nucleosome and its signaling abilities, which are mediated by the modifiable N-terminal tails. Prokaryotes, including both

eubacteria and archaea, have DNA binding proteins which, in the latter group, have a strong similarity to histones but lack the N-terminal tails and hence their signaling potential. He proposed that the emergence of eukaryotes one billion years ago, at a time when only prokaryotic life was present, was mainly influenced by the acquisition of histone octamers. The nucleosome is a structural and functional unit that allows gene expansion by protecting DNA against spontaneous compaction and preventing inappropriate transcription factor binding. It also underpins a range of epigenetic signaling systems that allow for the generation of multiple phenotypes from the same genotype, and lays the groundwork for multicellularity. The nucleosome also provides a connection from the genome to the environment and is, at the same time, responsible for the regulation of gene expression.

Peter Becker (Lüdwig-Maximilians University of Munich, Munich, Germany) described a highly sensitive mass spectrometry-based strategy to quantitatively monitor histone modification signatures. Dr. Becker's team applied this technique to try to establish the acetylation motifs on histones H3 and H4 in *Drosophila* cells. Systematic depletion of known histone acetyltransferases (HATs) and histone deacetylases (HDACs) allowed them to observe specific alterations of histone acetylation marks, clarify enzyme-substrate relationships, and evaluate the effect of the depletion in the overall acetylation level. Unexpectedly, global levels of acetylation were relatively unaffected by depletion of individual HATs, suggesting that there exists a minimal level of acetylation required to maintain nuclei stability. They also observed that lysine (K) acetyltransferase 6 (KAT6) was the only acetyltransferase responsible for almost 60% of global acetylation levels—a surprising result that still remains unpublished.

Ed Seto (Moffit Cancer Center, Florida, USA) elaborated on the importance of increasing the knowledge on HDACs substrates, due to the interdependent relationship that exists between them and the search for optimal HDAC inhibitors (HDACi). HDACi are potential anti-cancer drugs that are able to cause cell cycle arrest, revert cell transformation, and restrain tumor growth in animals. Dr. Seto's team performed an analysis of potential Sirtuin1 (SIRT1) substrates using proteomics techniques such as stable isotope labeling of amino acids in cell culture (SILAC). The study identified the human ortholog of *Drosophila melanogaster* male absent on the first (MOF), hMOF, which is a MYST family histone H4 lysine 16-specific acetyltransferase, as a SIRT1 substrate. Deacetylation of hMOF by SIRT1 inhibits its HAT activity. This promotes protein ubiquitination (K432/K444) and inhibits hMOF-mediated apoptosis and DNA repair activity in response to DNA damage through the acetylation of p53 at lysine 120.[2]

Acetylation, Chromatin Structure, and Gene Expression

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Tony Kouzarides (The Gurdon Institute, Cambridge, UK) shared with the audience the research from his lab that focuses on the identification of new small molecule inhibitors against HATs and HDACs for the treatment of cancer. He also talked about the pathways involved in the generation of newly discovered histone PTMs and the potential targeting of these PTMs for cancer therapies. Dr. Kouzarides presented bromodomain and extra terminal inhibitor (I-BET), an inhibitor of bromodomain-containing proteins, as a potentially effective drug for the treatment of mixed lineage leukemia (MLL)-fusion leukemia,[3] which is currently in clinical trials. With regards to the novel histone methylation pathways, he talked about the glutamine methylation of histone H2A by fibrillarin, which constitutes a RNA Polymerase I dedicated modification.[4] He also described the citrullination of arginine in histone H1, which is mediated by the enzyme peptidyl arginine de-iminase, type IV (PADI4). PADI4 is expressed in neutrophils and in stem cells, where it mediates the de-condensation of chromatin and appears to be overexpressed in malignant tumors. Finally, he reported on a yet unpublished novel histone methylation pathway that participates in DNA replication and involves H3K36me1 and H3K37me1, which are enriched at yeast DNA replication origins. Both PTMs are required for the synergistic binding of minichromosome maintenance complex component 2 (MCM2) to H3. Whereas K37me1 reduces this binding, K36me1 increases it. They searched for the enzymes that mediate this process and found that suppressor of position effect variegation enhancer of Zeste (Ez) and trithorax (Trx) 4 (SET4) deletion reduced H3K36me1 at DNA replication origins and delayed S-phase, while overexpression of SET4 induced cell proliferation. In human cells, MLL5 is a homolog of SET4 and its

knockdown reduces cell proliferation and induces cell cycle arrest at G1, providing a potential target for new MLL inhibitors.

Jerry Workman (Stowers Institute for Medical Research, Kansas City, USA) talked about histone acetyltransferase complexes. The general control of amino acid synthesis 5 (GCN5) subunit of Spt–Ada–Gcn5 acetyltransferase (SAGA) chromatin-modifying complex is responsible for sucrose non-fermenting (Snf2) acetylation. Snf2 acetylation, within switch of the mating type (Swi/Snf) chromatin remodeling complex, reduces the binding of this complex to acetylated nucleosomes and affects Swi/Snf complex genome wide occupancy.[5] Besides, HATs regulate the genomic dynamics of chromatin remodelers through acetylation of histones, acetylation of remodelers, and a possible competition between remodelers. Dr. Workman focused the last part of his talk on the role of enoki mushroom (Enok), the fly homolog of the human monocytic leukemia zinc finger protein (MOZ), YBF2, something about silencing-2 (SAS-2), TAT-interactive protein 60 (Tip60) (MYST3) acetyltransferase. Enok is expressed at high levels in embryos and localized to *spire* (spir) and *mael* (maelstrom) in oocytes. Moreover, Enok acetylates H3K23 in flies, playing a crucial role in oogenesis.

Colyn Crane-Robinson (University of Portsmouth, Portsmouth, UK) began his lecture by discussing his laboratory's initial undertaking: generating specific antibodies against acetylated histone residues. After performing ChIP experiments using anti-AcH4 and anti-AcH2A.Z antibodies, Dr. Crane-Robinson's team could confirm that both histone modifications frequently co-habit the same nucleosomes. Moreover, by using ChIP-Seq experiments they were able to show that AcH2A.Z is present at both active and poised (bivalent) transcription start signal (TSS), at enhancers and at insulators. He proposed the concept of H2A.Z, typically acetylated, as a general facilitator of nucleosome remodeling that allows access to chromatin by a wide variety of activating and repressing complexes.[6]

Lorraine Pillus (University of California San Diego, California, USA) described some aspects of MYST family proteins. KAT5 lysine acetyltransferase 5 (Tip60) is the human homolog of (essential SAS family (Esa1) acetyltransferase in yeast. Both enzymes are essential for cell viability, and genomic aberration of Tip60 is found in human carcinomas. Dr. Pillus presented that it is possible to rescue the phenotype of of *esa1*Δ cells by deletion of *SDS3*, which encodes a non-catalytic subunit of the reduced potassium depending 3 large (Rpd3L) deacetylase complex.[7] Furthermore, she reported that a new mark, H2A-pY57, is critical in casein kinase 2 (CK2) mediated transcriptional elongation which helps explain why earlier studies found the H2A-Y57A mutation to be lethal. The H2A-Y57F mutants affect histone modifications involved in transcriptional regulation.

Jean-Marc Victor (University of Pierre & Marie Curie, Paris, France) explained a physical view of the correlation between transcriptional activity and histone modifications through a mechanistic and spatial structure explanation based on allostery. The allostery in DNA and protein interactions can play an important role in gene regulation. He showed how the chromatin fiber provides a proof of principle for this model. The anchoring mode of DNA is controlled by the acetylation of H3, determining a clamped mode when the H3 tail is de-acetylated or, in contrast, a free hinged mode when it is acetylated. The spatial structure of chromatin determined by the acetylation of the tails of histones also determines the affinity of proteins that bind to DNA, thus modulating gene expression.

Astrid Hagelkruys (Medical University of Vienna, Wien, Austria) examined the impact of HDAC1 and HDAC2 isoform-specific functions in the development of the brain and epidermis. The deletion of 3 of the 4 HDAC1/HDAC2 alleles has a different phenotype, depending on the remaining allele and the organ affected. In the brain, normal development occurs when only one allele of HDAC2 is remaining, whereas mice with a single allele of HDAC1 die shortly after birth. In contrast, mice with a single allele of HDAC1 in the epidermis have a normal epidermal development, but when only one allele of HDAC2 has expressed spontaneous papiloma formation and hyperkeratosis is observed. Protein kinase C (PRKCδ), which is a direct target of HDAC2, is an important regulator of cell death, cell cycle progression, and energy metabolism, and its inhibition rescues the differentiation phenotypes of HDAC1Δ/+n HDAC2 Δ/Δn neurospheres. PRKCδ promoter hyperacetylation by HDAC2 is responsible

for this defective phenotype in the brain.[8]

James Davie (Manitoba Institute of Child Health, Manitoba, Canada) started his talk by describing a powerful chromatin fractionation method for chicken erythrocyte chromatin that had been previously elaborated in his lab. More recently, in combination with next generation DNA and RNA sequencing, it allowed them to define the organization of the chicken erythrocyte genome into chromosomal domains and obtain very useful information on the transcripts produced by these domains. In the second part of his talk, Dr. Davie focused on dynamic histone acetylation and RNA splicing. Histone deacetylases 1, 2) (HDAC1, HDAC2), and serine/arginine-rich splicing factor 1 (SRSF1) are involved in alternative splicing of the human myeloid cell leukemia sequence 1 (MCL1) gene. HDAC1/2 is recruited to *MCL1* pre-mRNA by splicing factors and, together with KAT2B and other lysine acetyltransferases (KATs), catalyzes histone acetylation of MCL1 gene and directly regulates its splicing.[9]

Rafael Casellas (NIAMS-NCI, National Institute of Health, Maryland, USA) discussed global chromatin acetylation and transcriptome amplification during lymphocyte activation. In G_0, there are mechanisms—such as limiting RNA Polymerase II recruitment and activity—that maintain the transcriptome at basal levels. Subunits of transcription factor II human (TFIIH) complex, including helicases involved in promoter melting, are generally downregulated in resting B cells (compared to activated B cells), and promoters are polymerase-loaded but unmelted. In contrast, when the immune response takes place, there is an increase in histone acetylation, promoter melting, and transcription across the genome in activated B cells, which correlates with the enhancement observed in the expression of TFIIH and Myc.[10]

Maribel Parra (Cancer Epigenetics and Biology Program, PEBC-IDIBELL, Barcelona, Spain) outlined the role of HDAC7 (histone deacetylase 7) in B lymphopoiesis. HDAC7 shows a lymphoid-specific expression pattern and is highly expressed in B lymphocytes, but not in myeloid cells such as macrophages. After reprogramming of pre-B cells intro macrophages by overexpression of C/EBPα, they found that HDAC7 shows a lymphoid-spedownregulated during the switch from pre-B cells to macrophages. However, reintroduction of HDAC7 causes de-repression of myeloid genes in pre-B cells and abolishes crucial functions of macrophages by interacting with the transcription factor myocyte enhancer factor 2C (MEF2C). In conclusion, Dr. Parra reported a novel role for HDAC7 as a lymphoid-specific transcriptional repressor of inappropriate genes in pre-B cells, which is required for their trans-differentiation to macrophages.[11]

Histone Acetylation in Physiology and Disease

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John Denu (University of Wisconsin, Wisconsin, USA) opened the session by talking about the relationship between deacetylation activity of sirtuins and metabolism. Dr. Denu's team has developed a quantitative mass spectrometry method to characterize the liver mitochondria acetyL-proteome during caloric restriction (in comparison to a control diet), in mice that lacked SIRT3 (versus wild type mice). Applying this technique, they observed that SIRT3 regulates mitochondrial metabolism, especially under caloric restriction by deacetylating proteins involved in several pathways of metabolism and mitochondrial maintenance.[12] Furthermore, SIRT6 is a tumor suppressor that controls cancer metabolism. In fact, SIRT6 KO mice show metabolic and degenerative phenotypes, and die by 4 weeks of age.[13] Free fatty acids are able to stimulate SIRT6 deacetylation activity, and myristic acid inhibits SIRT6 dependent de-myristoylation. These results suggest that fatty acids liberated from a fasting diet are able to condition SIRT6 activity, activating deacetylation and inhibiting de-myristoylation.

Eric Verdin (Gladstone Institutes, University of California, San Francisco, USA) discussed how natural metabolites can act as regulators of epigenetic enzymes, focusing on NAD+ and sirtuins. SIRT3 is exclusively located in mitochondria and regulates mitochondrial acetyl proteome. Dr. Verdin team compared the acetylation of lysines in liver mitochondria from SIRT3 KO mice vs. a wild type model using mass spectrometry, and found that 12% of the 16% acetylated lysines are regulated by SIRT3. In contrast, SIRT5 is a de-malonylase/de-succinylase *in vitro* and plays an important role in the regulation of fatty acid β-oxidation and plays an important role in the regulation of fatty acid e/de-succinylase

ylated lysinesDr. and sirtuins.ated sites in mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase 2 (HMGCS2). HMGCS2 is the rate-limiting step in β-hydroxybutyrate synthesis and it is deacetylated by SIRT3 in response to fasting[14]; SIRT5 regulates succinylation of this ketogenic enzyme.[15] In conclusion, SIRT3 is involved in the regulation of mitochondrial lysine acetylation, SIRT5 acts as a global regulator of lysine succinylation in mitochondria, and both sirtuins are involved in ketogeneis through regulation of HMGCS2.

Alejandro Vaquero (Cancer Epigenetics and Biology Program (PEBC-IDIBELL), Barcelona, Spain) presented several unpublished results about a new role of SIRT6 in the stress response mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). SIRT6 deacetylates H3K9 and regulates processes like telomere integrity and gene silencing, and it is the only sirtuin that causes an accelerated aging syndrome in KO mice. Most of this phenotype is due to hyperactivation of NF-kB pathway. Furthermore, SIRT6 interacts with the histone metyltransferase Suv39h1 set domain, but in contrast with SIRT1, loss of SIRT6 does not seem to alter Suv39h1 constitutive heterochromatin function. Interestingly, he described how SIRT6 overexpression induces mono-ubiquitination of 4 cysteines in the pre-set domain of suppressor of variegation 3–9 homolog 1 (Suv39h1), affecting cytoplasmatic signaling trafficking and avoiding the binding of this enzyme to chromatin. Mono-ubiquitination of Suv39h1 is related to proliferation, peaks at G1/S and G2/M, and is promoted by TNFα but not altered by other forms of stress. Dr. Vaquero's team proposed that S-phase kinase-associated protein 2 (SKP2) is the enzyme responsible for the mono-ubiquitination of Suv39h1 in the context of NF-kB pathway, and SIRT6 interaction and deacetylation promotes increased levels and activity of SKP2.

Lourdes Serrano (Rutgers University, New Jersey University, USA) outlined the role of SIRT7 in the maintenance of genome integrity, presenting results from an unpublished project by her team. She described how SIRT7 KO mice exhibit increased perinatal lethality, reduced life span, and an accelerated aging phenotype. SIRT7 protects cells from endogenous and induced DNA damage, and participates in the DNA damage response by regulating tumor protein p53 binding protein 1 (53BP1) recruitment to DNA double-strand break (DSB) during non-homologous end-joining repair (NHEJ). Moreover, SIRT7 is recruited to DSB to promote H3K18 deacetylation. Their results demonstrate that SIRT7 modulates 53BP1 through regulation of H3K8Ac levels at DSB.

Ömer Copur (Max Planck Institute of Biochemistry, Martinsried, Germany) presented also unpublished data of an analysis of *Drosophila* H4K16ac function *in vivo* using a genetic system to generate embryos or cell clones consisting of histone point mutations (i.e., H4K16A or H4K16R). Histone acetyltransferase Mof (males absent on the first) is present in the male-specific lethal (MSL) complex, where H4K16 acetyl mark regulates hyperactivation of single male X chromosome as dosage compensation. It is also present in nonspecific lethal (NSL) complex, where it is involved in the expression of the housekeeping genes. In order to elucidate the function of H4K16ac, Dr. Copur's team generated H4K16 mutant flies. Both males and females lacking H4K16ac die during embryogenesis, meaning that this mark is essential for development. In contrast, Mof mutant females but not males were able to survive to adulthood. Furthermore, the analysis of Mof and H4K16A mutant cell clones in developing *Drosophila* showed that clone growth in males but not in females is impaired in the absence of functional Mof. However, H4K16ac null mutant male and female cells were able to differentiate into respective tissues. This indicates that lack of H4K16ac does not lead to perturbation of developmental pathways. Finally, lack of H4K16ac alters heterochromatin protein 1 (HP1) and the pattern of H3K9me2 distribution in males without affecting chromatin in female nuclei.

Li-Huei Tsai (Howard Hughes Medical Institute, Chevy Chase, USA) presented data about the epigenomics of Alzheimer Disease (AD). Given that a decrease in histone acetylation is characteristic of several neurodegeneration processes in mouse models, she described how HDAC inhibitor sodium butyrate treatment is able to reinstate learning and memory, following neurodegeneration. HDAC2 is a critical negative regulator of genes essential for synaptic plasticity, learning, and memory,[16] and is induced by neurotoxicity and markedly upregulated in AD brain tissue. In fact, shRNA mediated HDAC2 knock down (K_D) in the hippocampus is sufficient to restore synaptic density and gene

expression, meaning that there exists an epigenetic blockade of learning and memory genes in the neurodegenerating brain.[17] Very interestingly, she explained how transcriptome profiling in brain tissue of human AD patients shows significantly altered gene expression not only of neuronal genes but also of several immune response genes. Surprisingly, genetic predisposition is related to immune functions, whereas non-genetic factors affect neural pathways.

Manel Esteller (Cancer Epigenetics and Biology Program, PEBC-IDIBELL, Barcelona, Spain) presented findings regarding the histone PTMs involved in cancer, and the potential epigenetic therapies targeting these marks. Histone modification profiles are altered in cancer, and it was recently observed that histone modifiers can also present genetic mutations. SETDB1 (SET domain bifurcated 1) methyl-transferase is amplified in lung cancer tumors. Silencing of SETDB1 gene by shRNAs significantly decreases tumor growth. Mithramycin could be used to treat patients with SETDB1 amplification, because is able to inhibit the binding of a transcription factor to SETDB1 promoter.[18] Another example is nuclear receptor binding SET domain protein 1 (NSD1), a histone methyltransferase, which is found methylated at the promoter in Soto's syndrome patients and in some tumors such as gliomas and neuroblastomas.[19] The current goal is finding new drugs that target epigenetic alterations in cancer, taking into account that the effect of epigenetic drugs will depend on the tumor type and its genetic and epigenetic features. Some examples of targeting epigenetic alterations in cancer include the use of HDAC inhibitors for the treatment of cutaneous lymphoma, 3-Deazaneplanocin A (DZNep) as an enhancer of Kruppel-like factor 2 (KLF2) expression—a tumor suppressor protein silenced by the histone methyltransferase enhancer of Zeste 2 (EZH2) in cancer,[20] and the CHR-6494 compound that was reported to be an inhibitor of the histone kinase Haspin.[21]

Beyond Histone Acetylation

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Shelley Berger (University of Pennsylvania, Philadelphia, USA) opened the session by reporting that p53 gain of function (GOF) mutants bind to epigenetic targets. p53 is mutated in more than 50% of human cancers. There are 6 “hot spot” mutations in p53 DNA binding domain that affect p53 function by altering the specificity of direct binding or altering its binding as a cofactor. p53 mutants do not bind correctly to the genome, and can bind to epigenetic targets, such as histone methyltransferase and acetyltransferase genes [mixed-lineage leukemia (*MLL*), monocytic leukemia zinc finger (*MOZ*)]. Knock down of p53 GOF mutants reduces histone methyl-transferase MLL expression and leads to a global reduction of H3K9me3 and H3K9Ac of the histone acetyltransferase MOZ. In general, p53 GOF mutants upregulate epigenetic pathways to activate oncogenic growth. Dr. Berger concluded her talk about unpublished data, remarking that p53 GOF mutant cells are "addicted" to epigenetic alterations.

Marian Martinez-Balbas (Molecular Biology Institute of Barcelona, Barcelona, Spain) reported on the involvement of histone methyl-transferase and demethylases in neural development. H3K27me3 increases during neurogenesis. Tri-methylation of H3K27 is catalyzed by EZH2 methyl-transferase, and JMJD3 (jumonji domain containing 3) demethylase is responsible for the removal of this mark. In addition, JMJD3 cooperates with SMAD family member 3 (SMAD3) to induce neural differentiation in neural stem cells (NSCs). This cooperation requires histone demethylase (HDM) activity. SMAD3 recruits JMJD3 to target promoters of transforming growth factor factor β (TGFβ), and JMJD3 is involved in TGFβ pathway by facilitating RNA Polymerase II elongation targeting promoters and binding enhancers in the genome—which finally results in the activation of genes in neural differentiation. Overall, Dr. Martinez-Balbas findings uncover the mechanism by which JMJD3 demethylase facilitates transcriptional activation.[22]

Tamara Maes (Oryzon genomics, Barcelona, Spain) presented 2 new drugs in development by the company Oryzon Genomics, a biotech company whose objective is the identification of new biomarkers and their exploitation in diagnostic assays—or their use as drug targets. Lysine specific de-methylase1A (LSD1) is a H3K4me2/me1 demethylase, the overexpression of which is associated with bad prognoses in cancer. Oryzon developed ORY-1001, a potent selective inhibitor of LSD1 which is now in phase I of clinical trials for acute myeloid leukemia (AML). The catalytic domain of the LSD proteins is highly homologous to that of the monoamine oxidase A and B enzymes (MAOA and MAOB). Because of this,

there are some MAO inhibitors such as tranylcypromine that can also inhibit LSD1.[23,24] However, ORY-1001 has better pharmacological properties; they are testing ORY-2001, a dual orally available LSD1/MAOB inhibitor, for use in the treatment of neurological disorders. It is able to restore neural capacity in senescence-accelerated mouse prone-8 (SAMP8) mice, a model of senescence that presents many pathological alterations reminiscent of Alzheimer disease.

Olivier Cuvier (LBME/CNRS, Toulouse, France) discussed how long-range contacts in chromatin can be mapped with high precision from combined ChIP-Seq and Hi-C data,[25] highlighting the role of insulator binding proteins (IBPs) and co-factors in long-range interactions and topological domains. IBPs further regulate chromatin locally through nucleosome dynamics by interacting with H3K36 histone methyltransferase nuclear receptor SET domain/*Drosophila* maternal effect sterile gene- 4 (NSD/dMes-4) that favors the recruitment of HATs. NSD/dMes-4 and Set2 methylate H3K36me2/3 respectively, thereby triggering H3K36me3-dependent nucleosome positioning co-transcriptionally. IBPs/dMes-4 further regulates H3K27me3 deposition at hundreds of gene promoters, unveiling a model showing how such factors control nucleosome dynamics, gene expression, and H3K27me3 spreading.[26]

David Landeira (University of Granada, Granada, Spain) reported a new role for jumonji AT-rich interactive domain 2 (Jarid2) in regulating planar cell pathways (PCP) required for embryonic stem cells (ESC) differentiation and early embryo development. Jarid2 is a component of the Polycomb Repressor Complex 2 (PCR2), which is involved in PCR2 recruitment and H3K27me3 deposition in ESCs, and plays an important role in ESC differentiation.[27,28] Jarid2-null ESCs express high levels of Nanog and low levels of non-canonical Wnt signaling components [wingless type 9a (Wnt9a), prickle homolog 1 (Prickle1), and frizzled class receptor 2 (Fzd2)]. Additionally, Jarid2 regulates a subset of planar cell polarity (PCP) genes, meaning that Jarid2 null cells are not able to differentiate properly or to self-organize in coherent colonies.

Disclosure of Potential Conflicts of Interest

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No potential conflicts of interest were disclosed.

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