Chromatin and the cell cycle meet in Madrid

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At the end of June 2008, researchers from diverse fields, ranging from chromatin remodeling to cell cycle control, gathered in Madrid at a Cantoblanco Workshop entitled ‘Chromatin at the Nexus of Cell Division and Differentiation’. The work discussed at this meeting, which was co-organized by Crisanto Gutierrez, Ben Scheres and Ueli Grossniklaus, highlighted the emerging connections that exist between cell cycle regulation and chromatin in both animals and plants.

Introduction
Chromatin, which consists of DNA and its associated histone proteins, duplicates during cell division. In contrast to the impressive amount of knowledge that exists on the regulation of the cell cycle and DNA replication, relatively little is known about the replication of other chromatin components. The factors that influence cell cycle replication and chromatin assembly must be connected in order to coordinate these events, and recent studies have highlighted how cell cycle regulatory mechanisms both control and respond to chromatin modifications. As a consequence, chromatin states regulate the capacity of cells to divide and thus have a strong influence on embryonic development, organogenesis, adult tissue homeostasis, aging and diseases such as cancer. As organisms develop, their chromatin is gradually modified as cell divisions progress and differentiation takes place. The transmission of life through sexual reproduction, therefore, implies a return to the original chromatin state in the zygote or early embryo. Such nuclear reprogramming might also depend, in part, on cell cycle progression.

A number of the talks at the Madrid meeting illustrated the complex and intricate relationships that exist between cell cycle regulators and the chromatin-modification machinery. Indeed, a highlight of the meeting was the number of connections that emerged among cell cycle regulators, transcription factors and chromatin modifiers. As we discuss in more detail below, the meeting focused on areas such as the role that Retinoblastoma (Rb) plays in controlling DNA methylation and the histone modifications that accompany the cell cycle.

Cycles of chromatin modifications
Kinetochore protein complexes at eukaryotic centromeres are responsible for correct chromosome segregation during nuclear divisions. Kinetochore formation is regulated by the substitution of the common form of histone H3 (H3.1) by the centromeric histone H3 variant CENH3 within centromeric nucleosomes. In contrast to the deposition of H3.1 in regular nucleosomes, which occurs during S phase, CENH3 is incorporated after anaphase in human (Jansen et al., 2007) and Drosophila melanogaster (Schuh et al., 2007) cells.

Surprisingly, CENH3 loading onto the kinetochore has been observed in plants during (late) G2 of interphase, when two sister kinetochores become detectable (Lermontova et al., 2006; Lermontova et al., 2007). Ingo Schubert (Leibniz Institute of Plant Genetics and Crop Research, Gatersleben, Germany) further discussed his work on the targeting of CENH3 to Arabidopsis centromeres, which requires just the histone-fold domain of the C-terminal part of CENH3. In Arabidopsis, partial RNAi-mediated depletion of CENH3 causes dwarfism, probably resulting from a reduced number of mitotic divisions. To our knowledge, this is the first report of an organism able to tolerate the loss of CENH3. Using this genetic material, it should be possible to examine the potential role of CENH3 as a carrier of epigenetic inheritance, as proposed by Steve Henikoff (Henikoff and Ahmad, 2005).

The epigenetic inheritance of chromatin modifications rests on the supposed semi-conservative inheritance of histone-modification patterns through cell divisions. This hypothesis has been proposed for a number of covalent modifications on heterodimers of histones H3 and H4 (Ahmad and Henikoff, 2002) and has been extended to histone H3 variants, CENH3 and H3.3 (Hake and Allis, 2006). However, the semi-conservative replication of an epigenetic pattern has only been demonstrated for DNA methylation, which occurs at cytosine residues (Chan et al., 2005). In plants, DNA methylation is also propagated from one generation to the next through meiosis (Kakutani et al., 1999; Saze et al., 2003). Vincent Colot (Ecole Normale Supérieure, Paris, France) reported the inheritance of a large sample of hypomethylated sequences that results from the loss of DECREASED DNA METHYLATION 1 (DDM1) function in Arabidopsis. His lab has followed, from the initial cross between ddm1 and wild-type plants, the progeny of plants that no longer carry the ddm1 mutation for up to eight generations. Remarkably, although they found stable hypomethylation at some loci, consistent with previous observations (reviewed by Richards, 2006), they observed efficient and faithful remethylation at others. Further analysis of this process suggests that the RNAi-dependent machinery has an essential role in the remethylation of certain loci. Such DNA remethylation was observed after demethylation had been induced by the loss of the MAINTENANCE METHYLTRANSFERASE 1 (MET1) gene (Mathieu et al., 2007). Vincent Colot’s findings further identify different classes of loci according to their capacity to remethylate, leading to the potential definition of elements in the genome that are essential for the nucleation of de novo DNA methylation.

The semi-conservative nature of DNA methylation maintenance implies that DNA methylation is coupled to the DNA replication fork. How this is achieved has remained a long-standing question. Steve Jacobsen (Howard Hughes Medical Institute, UCLA, Los Angeles, USA) reported his lab’s study of the ORTHrus 2 (ORTH2) [also known as VARIANT IN METHYLATION 1 (VIM1)] family, which includes several proteins with a SET domain and a RING finger-associated (SRA) domain that recognizes hemi-methylated DNA. This protein family is absent from yeast and Drosophila, but is conserved in mammals. The mammalian nuclear protein 95 (Np95; Uhrf1) contains an SRA domain and belongs to a large complex that includes DNA methyltransferase 1 (Dnmt1) and proliferating cell nuclear antigen (Pcna) and that probably couples DNA methylation activity to DNA replication (Jansen et al., 2007; Sharif et al., 2007). In Arabidopsis, CpNpG motifs are methylated by a plant-specific methyltransferase, CHROMOMETHYLASE 3.
A specific member of the ORTHRUS family is involved in recruiting CMT3 to CpNpG motifs (Johnson et al., 2007). Steve Jacobsen also presented an analysis of the role of other members of the ORTHRUS family, leading to the idea that each member of this family might couple the maintenance of DNA methylation to each type of DNA methyltransferase. These studies, together with reports from Eric Richards' team (Woo et al., 2008; Woo et al., 2007), pave the way to further our understanding of the propagation of DNA methylation patterns through cell division. It is also possible that the semi-conservative nature of the propagation of DNA methylation extends to cytosine DNA methylation in non-CpG sequence contexts that are specific to plants (i.e. at CpNpG and CpHpH).

Centromeres are not only marked by the deposition of CENH3, but also by extensive DNA methylation at repetitive elements and transposons (Lippman et al., 2005; Lister et al., 2008). Until now, the status of DNA methylation has been studied during interphase, but the condensation of chromatin required through mitosis could interfere with the heterochromatic status of centromeres. Rob Martienssen (Cold Spring Harbor Laboratory, New York, USA) reported his studies in yeast that aim to correlate the cell cycle with modifications to heterochromatin composed of transposable elements and repeats. Small interfering RNAs produced by transposable elements are rapidly turned over through the combined action of the DNA- and RNA-dependent RNA polymerases and Argonaute. RNAi is linked to the histone methyltransferase Clr4, which dimethylates histone H3 at lysine (K) 9 and is responsible for the heterochromatin state. This status, however, is unstable during the cell cycle, as chromosomal replication causes the transient loss of heterochromatin. Heterochromatic transcripts then accumulate following the phosphorylation of histone H3 at serine 10 in mitosis, and then, during S phase, heterochromatin reassembles (Kloc et al., 2008). The retention of cohesin by heterochromatin in G2 promotes the chromosome condensation that is necessary to proceed through mitosis. This cyclic mechanism allows the epigenetic inheritance of centromeric heterochromatin to occur through cell division.

Maria Blasco (CNIO, Madrid, Spain) also reported an unsuspected link between the small non-coding RNA machinery and DNA methylation. DNA methylation levels decrease in response to decreased Dicer1 activity in a mouse cell line. The lack of Dicer1, an RNase III-family nuclease essential for generating mature microRNAs, appears to downregulate the levels of microRNAs from the miR-290 cluster. The retinoblastoma-like 2 protein (Rbl2) is a direct target of the miR-290 cluster and represses transcription of the de novo DNA methyltransferases Dnmt3a and Dnmt3b. As a result, the downregulation of miR-290 by low Dicer1 levels correlates with the reduced expression of these two de novo methyltransferases, and the resulting decreased DNA methylation levels cause aberrant telomere elongation and increased telomere recombination (Benetti et al., 2008).

**Cell cycle controls chromatin modification**

In addition to the association of the cell cycle machinery with the maintenance of different chromatin states, there is also increasing evidence that cell cycle regulators directly control chromatin modifications (see Fig. 1). Fred Berger (Temasek Life Sciences Laboratory, Singapore) reported at the meeting that the transcriptional inhibition of the maintenance DNA methyltransferase *METI* by Retinoblastoma (Rb) is conserved in plants. The imprinted genes *FLOWERING LOCUS A* (*FWA*) and *FERTILIZATION INDEPENDENT SEED 2* (*FIS2*) are expressed only from their maternal allele. The parent-specific expression of each allele of these genes is presumably controlled by the DNA methylation status of their promoters in male and female gametes (Jullien et al., 2006a). The repression of *METI* expression by Rb during female gametogenesis leads to the DNA demethylation that is essential for the expression of the *Arabidopsis* imprinted genes (Jullien et al., 2008). The link between Rb and imprinting involves additional regulation, as the Polycomb group protein FIS2 controls other imprinted genes, including *MEA* (Jullien et al., 2006b) and *PHERESI* (Makarevich et al., 2008). The transcriptional repression of *METI* during female gametogenesis suggests that a genome-wide demethylation of DNA might occur, which is surprising because DNA methylation patterns are transmitted through generations in plants.

The *Arabidopsis* root is a key model system for the study of plant development and stem cells because the number and arrangement of stem cells around the niche are highly reproducible and many cell-identity markers are available. Ben Scheres (University of Utrecht, Utrecht, The Netherlands) reported on the regulation of stem cell maintenance by Rb. Rb binds to a transcription factor that functions in the root stem-cell niche, and Rb loss, concomitant with the overexpression of another transcription factor called PLETHORA, causes a massive expansion of root stem cells (Grieneisen et al., 2007; Wildwater et al., 2005). In addition, synergistic effects between the Rb pathway and the Chromatin assembly factor 1 (Caf1) pathway, which is involved in histone H3 and H4 deposition, have been observed. These findings suggest that Rb directly regulates cell fate via the recruitment of transcription factors and perhaps through chromatin remodeling caused by the deposition of unmodified H3 variants.

![Fig. 1. Known and hypothetical controls linking the cell cycle and chromatin modification.](image)

The controls of the G1–S phase transition of the cell cycle (blue circles) regulate DNA methylation and histone modifications (dark-purple hexagons), which also regulate each other. Nucleosome assembly (green) onto newly replicated DNA at the replication fork is depicted. DNA methylation (light-purple hexagon) is replicated in a semi-conservative manner. Whether histone modifications are transmitted through cell division in a semi-conservative manner remains a matter of debate. During the S phase, replication-coupled histone replacement (orange box) is likely to play a role in chromatin dynamics. The G2–M transition is also correlated with histone modifications. During the G2 and G1 phases, non-replicative histone replacement (orange box) might play a role in chromatin dynamics, which could be important for the decision whether to enter a new replication cycle or to differentiate.
Crisanto Gutierrez (Centro de Biologia Molecular ‘Severo Ochoa’, CSIC-UAM, Madrid, Spain) reported on his lab’s study of the regulation of root development by the GLABRA 2 (GL2)-expression modulator (GEM), which interacts with CDT1, a pre-replication complex component that is involved in the licensing of DNA replication, and with TRANSPARENT TESTA GLABRA 1 (TTG1), a transcriptional regulator of epidermal cell fate. In the epidermis, GEM controls the level of histone H3K9 methylation at the promoters of the GLABRA 2 and CAPRICE (CPC) genes, which are essential for epidermis patterning (Caro et al., 2007). These results are strikingly reminiscent of the dual function played by geminin in animal cells (Caro and Gutierrez, 2007). In fact, GEM turns out to be a master regulator of cell division in different root cell types. Thus, both GEM and geminin in plants and animals, respectively, have the potential to regulate proliferation-differentiation decisions by integrating DNA replication, cell division and transcriptional controls.

Other types of chromatin remodeling machinery also have an impact on cell proliferation, as shown by Doris Wagner (University of Pennsylvania, Philadelphia, USA). The Arabidopsis genome encodes four SWI/SNF ATPases. Loss-of-function analyses have shown that SWI/SNF ATPase activity is required for stem cell maintenance in the shoot, where the SWI/SNF ATPases bind to the promoters of WUSCHEL, which is essential for stem cell maintenance, and CUP-SHAPED COTYLEDON (CUC), which is involved in setting the boundaries of proliferation zones. In the flower meristem, the SWI/SNF ATPases target other regulators of cell proliferation, AGAMOUS (AG) and APETALA 3 (AP3). These results highlight the role of chromatin remodeling ATPases in the control of organ size in plants (Bezhani et al., 2007; Kwon et al., 2006). Collectively, these studies reveal that ubiquitous cell cycle regulators can have specific impacts in particular cell types on the global status of chromatin. This type of regulation might be considered as having a licensing activity that allows the establishment of expression patterns required for correct terminal cell differentiation.

**Chromatin controls cell cycle regulation**

Until recently, cancer was considered to be a disease that is driven by genetic abnormalities. However, research in recent years indicates that epigenetic alterations of gene expression represent a major source of tumorigenesis (Lund and van Lohuizen, 2004). In vitro studies of DNA methylation and histone modifications in cancer cells have successfully identified epigenetic mechanisms that contribute to cancer initiation and progression, but in vivo studies of chromatin modifications and other epigenetic processes in cancer remain scarce. Maria Dominguez (Instituto de Neurociencias UMH-CSIC, Alicante, Spain) opened the discussion of the influence of aberrant chromatin on cancer using the Drosophila model system. She described the identification of two novel Polycomb group (PcG)-related repressors, Pipsqueak and Lola. When coupled with a hyperactivation of the Notch signaling pathway, the deregulated expression of these epigenetic repressors promotes the development of highly invasive tumors that are associated with the epigenetic silencing of Rh (Rhβ) (Ferre-Marcó et al., 2006). The formation of these invasive tumors depends on the chromodomain protein Polycomb (Pc) and on the histone-modifying enzymes Enhancer of zeste [E(z)] (the Drosophila homolog of the human EZH2 oncogene) and Histone deacetylase 1 (Hdac1; Rd3). The genetic inactivation of Pc, E(z) or Rd3, or the pharmacological inhibition of histone deacetylases, completely reverses the tumor invasion phenotype, probably by preventing the aberrant silencing of genes that contribute to abnormal proliferation. Maria Dominguez also suggested that the deregulation of Pipsqueak might promote uncontrolled proliferation and inhibit cell differentiation (leading to tumorigenesis) by depleting histone variant H3.3, which is present at active chromatin sites, through interactions with ubiquitin ligase components. These findings suggest a model in which the targeted degradation of the histone H3.3 variant, and of other chromatin targets, by deregulated Pipsqueak-ubiquitin ligase complexes might help to convert active chromatin into silent chromatin, leading to aberrant gene silencing patterns.

PcG repressors are required for the maintenance of transcriptional gene repression patterns (cellular memory), and their upregulation is considered to be a key step towards malignancy in several carcinomas. As such, several PcG genes (including HPC1 and EZH2) are considered to be proto-oncogenes (Lun and van Lohuizen, 2004). One of the most surprising talks at the meeting, by Giacomo Cavalli (Institute of Human Genetic, CNRS, Montpellier, France), concerned the direct association of PcG mutations and cancer. Cavalli continued the discussion of the key role of PcG proteins in the heritable maintenance of cell fate and in the regulation of cell proliferation in Drosophila. His lab’s genome-wide studies have shown that these epigenetic repressors bind to and regulate a variety of key developmental genes (Schuettengruber et al., 2007). As a consequence, loss-of-function mutations in PcG genes are lethal during embryogenesis. In order to analyze later stages of development, the Cavalli group induced clones of homozygous mutant cells in larval tissues. Strikingly, besides derepressing known targets, such as the Hox genes, these PcG gene mutations could induce malignant tumors characterized by altered Notch signaling, demonstrating a link between epigenetic regulation by Pc proteins and Notch-mediated proliferation control.

Margaret Fuller (Department of Developmental Biology, Stanford University School of Medicine, Stanford, USA) presented her group’s work on epigenetic regulation at the transition from proliferation to terminal differentiation in the Drosophila male germline (Fuller and Spradling, 2007). Short-range signals from the germline stem cell niche are responsible for sustaining proliferating stem cells. Margaret Fuller showed that subunits of Polycy repressive complex 2 (PRC2) are expressed in stem cells and in precursor cells undergoing transit-amplifying divisions, but the PRC2 components Su(z)12 and E(z) are both abruptly downregulated after the switch to differentiating spermatocytes occurs. At that point, Pol II transcriptional machinery is recruited to the promoters of terminal differentiation genes and cell type-specific components of the initiation machinery are expressed and act to turn on the transcriptional program for spermatid differentiation. Thus, the maintenance of repression of differentiating genes might be a key mechanism by which the epigenetic repressors, Pc and PRC2, maintain ‘stemness’ and promote cell proliferation (Fig. 2). An important unresolved question is how PRC2 expression is downregulated during germline stem cell development.

The existence of PcG complexes that are distinct from the ‘classical’ PRC2 and PRC1 complexes provides a plausible explanation for the opposing effects on cell proliferation and tumorigenesis that have been observed following the genetic depletion of individual PcG genes in mice (Lessard et al., 1999). Examples of ‘unconventional’ PcG complexes were also highlighted in the talks of Maria Dominguez and Giacomo Cavalli. Elucidating the composition and in vivo function of different species of PRC complexes is of prime importance given the fundamental role of PcG proteins in epigenetic inheritance and given the connections that exist between epigenetic inheritance and cancer.
The sub-functionalization of PRC complexes by additional components might occur not only in animals but also in plants, according to results presented by Pedro Crevillen from Caroline Dean’s group (John Innes Centre, Norwich, UK). Prolonged exposure to cold is required to induce flowering in *Arabidopsis* and in many other annual plants, which spend winter as a rosette of leaves and flower in spring. In cold-treated rosettes, the *Arabidopsis* PRC2 associates with two plant homeodomain (PHD)-type zinc-finger proteins, VERNALIZATION 5 (VRN5) and Extra sexcombs (Es) (VRN3) methylate histone H3 at lysine 27, and this epigenetic mark is recognized and bound by the chromodomain-containing protein Pc/HPC (green oval), a component of PRC1, to form stable, repressive chromatin. Other forms of PRC (purple) have been detected and may instead repress cell proliferation and favor differentiation. The dynamic formation of distinct isoforms of PRC complexes may help to define the dynamic reprogramming of the genome at the transition from proliferation to differentiation. How PRC2 and PRC1 are recruited to specific genes remains poorly understood.

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These new results illustrate once more, the remarkable conservation of epigenetic mechanisms between plants and animals. Conventional PRC2 complexes include several members of the E(z) and Su(z)12 families, and it remains to be established whether the PHD factors also participate in other functions that involve PRC2, such as the production of inflorescence and seed development, both essential for crop yield.

**Chromatin, reprogramming and pluripotency**

From a developmental perspective, the link between cell proliferation and chromatin is tightly embedded in the mechanisms that control the balance between stem cell identity and fate commitment, as the number of cell divisions is tightly controlled during lineage differentiation in the embryo. This is essential for the proper determination of organ size and for the temporal and spatial coordination of embryogenesis.

Konrad Hochedlinger (Harvard Stem Cell Institute, Boston, USA) discussed the molecular mechanisms of reprogramming adult cells as a tool for generating embryonic stem (ES)-like cells called induced pluripotent (iPS) cells. One obstacle to this approach is that the reprogramming of somatic cells through the overexpression of the four transcription factors Oct4 (Pou5f1), Sox2, c-Myc and Klf4, occurs at low frequency (less than 0.1%) and genome reprogramming can be incomplete. As Hochedlinger discussed, these rates can be improved by either selecting for cells that have reactivated Nanog or Oct4 (Maherali et al., 2007), or by temporally controlling the expression of the reprogramming factors using inducible transgenes (Stadfeld et al., 2008). Hochedlinger also discussed results which suggest that reprogramming might be a universal process, as neural progenitor cells (Eminli et al., 2008) and terminally differentiated pancreatic beta cells (Stadfeld et al., 2008) can both be reprogrammed into iPS cells by expressing the above four transcription factors. The sequential silencing of somatic genes and the activation of embryonic genes might involve interactions, or cooperation, among Oct4, PRC2 and other PcG proteins.

Wolf Reik (Babraham Institute, Cambridge, UK) added to the discussion of epigenetic reprogramming and pluripotency and presented collaborative work with Myriam Hemberger’s lab (Farthing et al., 2008). In the early mammalian embryo, genome-wide DNA demethylation is assumed to confer pluripotency and is followed by de novo methylation in cells of the inner cell mass, which produce the embryo proper. Their global profiling of DNA methylation in sperm cells, ES cells and trophoblast stem cells revealed some surprising observations. Although sperm cells are differentiated, their DNA methylation profile was similar to that of pluripotent ES cells. However, some loci remained highly methylated and consisted of key markers of pluripotency. These observations indicate that the sperm genome has been cryptically reprogrammed but has not reached a pluripotent state. The pluripotent state is achieved by further demethylation of the sperm genome after fertilization. Demethylation of mouse ES cells [by knocking out Dnmt1 or the Dnmt1-recruiting Np95] allows them to differentiate into trophoblast cells, something normal ES cells cannot do. Genome-wide profiling led to the identification of a trophoblast transcription factor that is epigenetically silenced in the embryonic cell lineage.

It is thus apparent that in mammals, DNA methylation (and other related chromatin modifications) sets a global chromatin structure that directly contributes to early cell lineage decisions or that regulates a set of transcription factors that control key commitment events in early lineage differentiation, notably the distinction between the embryo proper and the trophoblastic lineage of the placenta. In plants, similar to mammalian early embryogenesis, two lineages give rise to the embryo proper and to a nutritive embryo annex, the endosperm. Whether this early distinction between the
two cell-lineages also involves DNA methylation is not clear. Parental imprinting has only been detected in the endosperm, suggesting a specific epigenetic regulation of the lineage that leads to the development of this nutritive embryo annex, reminiscent of what happens in the mammalian trophoblastic lineage (Feil and Berger, 2007). The differentiation between the two lineages could also occur after fertilization, as in mammals, by the differential reactivation of the paternal genome in the embryo and in the nutritive embryo annex. During early embryogenesis in animals, the activation of parental genomes that occurs after fertilization requires large-scale epigenetic reprogramming and relies on maternally stored factors. In higher plants, the picture is more controversial. Maternal-effect genes, some of which are regulated by genomic imprinting, illustrate the importance of maternal control in seed development. Moreover, studies in Arabidopsis (Vieille-Calzada et al., 2000) and maize (Grimanelli et al., 2005) have shown that for many genes, no transcripts derived from the paternal allele can be detected during the first few days after fertilization, suggesting widespread maternal controls. However, the early presence of paternally derived transcripts has been demonstrated for several loci (Meyer and Scholten, 2007; Weijers et al., 2001), suggesting that the requirement for the initiation of paternal transcriptional activity might differ on a gene-by-gene basis. Ueli Grossniklaus (Institute of Plant Biology, University of Zurich, Switzerland) presented a collaborative project with Daniel Grimanelli to study the regulation of paternal genome activation. Genes with very early paternal expression were activated gradually, with each of the loci studied showing a distinct timing and kinetics of paternal activation. Genetic studies using maternal mutants in various epigenetic regulators defined pathways that either repress or activate paternal alleles. These studies identified maternal factors that might control chromatin organization and regulate the transcriptional status of paternal alleles in plants. Whether the regulation observed for a few loci occurs genome-wide and equally in the embryo and the endosperm remains to be determined.

Concluding remarks

The Cantoblanco Workshop on ‘Chromatin at the Nexus of Cell Division and Differentiation’ in Madrid brought together, for the first time, plant and animal researchers from the chromatin field to discuss how the cell cycle both controls and is influenced by chromatin. Together, the studies in plants and animals that were presented indicate that a very tight and complex dialogue takes place between key cell cycle regulators and chromatin modifications. A key finding presented at the meeting was that the transcriptional regulation of cell cycle control genes by chromatin remodeling and conversely other epigenetic processes, particularly PcG regulation, controls the rate of cell division in a cell-specific manner, and is essential for normal organogenesis and to prevent tumorigenesis. The link between the cell cycle and chromatin is at the heart of the epigenetic memory associated with the covalent modifications of DNA and histones that are transmitted in a semi-conservative manner at the DNA replication fork. Key recent findings reported at the meeting have clarified how DNA methylation is propagated in a semi-conservative manner, but how histone-modification patterns are maintained through cell divisions remains unclear (Fig. 1). The balanced regulation of the number of cell divisions and the propagation of chromatin modifications gradually defines the global transcriptional status of cells and their degree of differentiation. It is, however, as yet unclear whether one will be able to read the fate of a cell from a genome-wide map of its histone modifications, but cell type-specific epigenetic maps and cancer epigenomes will represent a major advance in the near future towards identifying new disease genes and potential targets for therapeutic intervention. In the germline and early embryo, the epigenetic marks of differentiation have to be reset. Elucidating how this is achieved presents a major challenge for future years, as the molecular machines that remove histone methylation, which was until recently considered to be a stable epigenetic mark, are not well characterized, and the role of histone demethylation/methylation is barely understood. Although in vitro culturing studies have been very helpful in identifying epigenetic mechanisms responsible for reprogramming, the problem of resetting the epigenetic modifications now needs to be addressed directly, using whole organisms. The remarkable conservation in chromatin regulation between plants and animals will enable researchers to exploit the strengths of each model to decipher, in vivo, the molecular mechanisms that underlie chromatin dynamics and its impact on the coordination of cell division, cell fate determination and differentiation during normal development and disease.

References


