Conference Scene

Epigenetics Europe 2011

Epigenetics Europe Conference Munich, Germany, 8–9 September 2011

At the Epigenetics Europe conference in Munich, Germany, held on 8–9 September 2011, 19 speakers from different European countries were presenting novel data and concepts on molecular epigenetics. The talks were mainly focused on questions of the generation, maintenance, flexibility and erasure of DNA methylation patterns in context of other epigenetic signals like histone tail modifications and ncRNAs.

The meeting was opened by Walter Doerfler (University of Cologne, Cologne, Germany), one of the early researchers studying the role of DNA methylation in mammals. His group studied DNA methylation changes stimulated by adenoviral infection [1] and showed already more than 30 years ago that DNA methylation inhibits gene transcription [2]. Walter Doerfler illustrated the process of epigenetic pattern generation by the piling up of birds on electricity wires. Individual birds may sit next to each other or leave some difference distance between them, thereby generating a pattern. New ones may join, others may leave and occasionally all may fly away to return later to generate the same or a new pattern. This model summarizes all the events relevant for the study of DNA methylation, how patterns are generated and altered by *de novo* DNA methylation and demethylation, and how they are maintained after DNA replication. While the principles of pattern generation and modification are still largely not understood, a mechanism is known for how existing methylation patterns can be propagated through cell division. This is based on the fact that DNA methylation mainly occurs at CpG sites where both DNA strands are methylated in a symmetrical fashion. Replication converts the fully methylated DNA into a hemimethylated state, in which only one strand of the CpG site carries a methyl group. This state is recognized by the maintenance methyltransferase DNMT1 and specifically methylated, such that the original pattern is restored. Two other members of the DNMT family, DNMT3a and DNMT3b, do not show specificity for methylation of hemimethylated CpG

sites and are mainly involved in *de novo* DNA methylation [3].

Frank Lyko (German Cancer Research Center, Heidelberg, Germany) reported novel data from detailed genome-wide methylation analyses on the variability of DNA methylation patterns showing that interindividual variance is much smaller than tissue variance indicating that changes in methylation patterns are involved in differentiation [4]. Jörn Walter (Saarland University, Saarbrücken, Germany) presented novel results from the methylation analysis of repeat elements from human cells. Using a technical trick, they were able to determine whether individual CpG sites are fully methylated, hemimethylated or unmethylated, which allowed modeling the process of DNA methylation. By using different DNMT-deficient cell lines, the individual roles of the different DNMTs could be studied. The resulting data provided strong evidence that DNMT3 enzymes – together with DNMT1 – are involved in the preservation of DNA methylation levels at repeats. The specific methylation of repeats by DNMT3 enzymes is possible, because they are mainly localized at heterochromatic repeats as initially proposed by Peter Jones [5]. Albert Jeltsch showed that the heterochromatic localization of DNMT3a depends on the multimerization of DNMT3a and binding of DNMT3a fibers to more than one DNA molecules oriented in parallel [6,7]. The methylation data presented by Jörn Walter also showed that DNMT3 enzymes are responsible for non-CpG methylation observed in embryonic cells first time by Lister *et al.* [8]. In agreement with this model, the expression levels of

Albert Jeltsch

Jacobs University Bremen, Campus Ring 1,
28759 Bremen, Germany
and
Institute of Biochemistry, Stuttgart University,
Pfaffenwaldring 55, 70569 Stuttgart, Germany
albert.jeltsch@ibc.uni-stuttgart.de

DNMT3 enzymes are high in embryonic cells [9], and they have been shown to have non-CpG activity *in vitro* [10]. Interestingly, DNMT3a and DNMT3b showed different preferences (so far not understood) for the methylation of some non-CpG sites. The biological role of this non-CpG methylation is unclear at present.

Different talks were addressing the variability of DNA methylation focusing on the influence of the environment. Karen Lillycrop (University of Southampton, Southampton, UK) described data on the influence of postnatal conditions [11]. It has been speculated that developing embryos may be preadapted for their environment by epigenetic changes induced by nutritional state. Cornelia Toelg (Hospital for Sick Children, Toronto, Canada) reported on the effects of bacterial infection on DNA methylation where persisting changes of the cellular physiology in response to repetitive infections were observed as well. Frank Lyko reported that only small changes in DNA methylation occur during aging [4]. It appeared that in all these cases the exact causal and molecular connection between physiological changes and methylation changes were still elusive.

DNA methylation does not occur on naked DNA. Robert Feil (Institute of Molecular Genetics, CNRS, Montpellier, France) and Albert Jeltsch reported how DNA methylation signals are generated in response to histone modification patterns. Albert Jeltsch showed data how the ADD and PWWP domains of DNMT3a are involved in the reading of the absence of methylation at H3K4 and presence of trimethylation at H3K36 [12,13]. Hence, DNMT3a directly responds to the distribution of these two marks, which are mutually exclusive. While this, at first instance, does not appear to solve the problem of how methylation patterns are generated, because one pattern is just prepared following another one, Jo Peters (MRC Harwell, Harwell, UK) presented results that may cut this Gordian knot. She reported that the transcription of long noncoding antisense RNAs triggers *de novo* methylation of promoters in sense direction [14]. Transcription coupled deposition of H3K36me3 read by the

PWWP domain of DNMT3a may be one mechanism to explain and connect these findings providing a first molecular model of how expressional activity could be converted into DNA methylation.

Another chromatin related talk was given by Irina Stancheva (University of Edinburgh, Edinburgh, UK), who reported on work on the LSH chromatin remodeling factor, which is necessary for *de novo* DNA methylation [15], and also has a role in DNA repair. Chromatin dynamics were also addressed by Fred V Leeuwen (Netherlands Cancer Institute, Amsterdam, The Netherlands), who showed that histones are readily exchanging, which increases the need of mechanisms to maintain certain modification patterns. He also showed that during passage of the RNA and DNA polymerases histones were moved downstream, such that old histones accumulate at the 3' end of genes. In addition, he provided evidence that H3K79me3 accumulates in old histones, such that this may represent a mark of the age of a certain nucleosomes [16].

Finally, the removal of DNA methylation was discussed and Paul Cloos (Copenhagen University, Copenhagen, Denmark) and Jörn Walter provided evidence that hydroxylation of 5-methylcytosine by TET enzymes acts as an antagonist of DNA methylation. Jörn Walter reported that in the early zygote the long known loss of 5-methylcytosine in the paternal genome, at least partially, is due to the conversion into 5-hydroxymethylcytosine, which remains stable afterwards [17]. Paul Cloos reported on the genome-wide determination of TET1 binding sites [18] and the discovery of CXXC5, a putative novel regulator of TET enzymes.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Gunthert U, Schweiger M, Stupp M, Doerfler W. DNA methylation in adenovirus, adenovirus-transformed cells, and host cells. *Proc. Natl Acad. Sci. USA* 73(11), 3923–3927 (1976).
- 2 Sutter D, Doerfler W. Methylation of integrated adenovirus type 12 DNA sequences in transformed cells is inversely correlated with viral gene expression. *Proc Natl Acad. Sci. USA* 77(1), 253–256 (1980).
- 3 Jurkowska RZ, Jurkowski TP, Jeltsch A. Structure and function of mammalian DNA methyltransferases. *Chembiochem* 12(2), 206–222 (2011).
- 4 Bocker MT, Hellwig I, Breiling A, Eckstein V, Ho AD, Lyko F. Genome-wide promoter DNA methylation dynamics of human hematopoietic progenitor cells during differentiation and aging. *Blood* 117(19), e182–e189 (2011).
- 5 Jones PA, Liang G. Rethinking how DNA methylation patterns are maintained. *Nat. Rev. Genet.* 10(11), 805–811 (2009).
- 6 Jurkowska RZ, Rajavelu A, Anspach N *et al.* Oligomerization and binding of the Dnmt3a DNA methyltransferase to parallel DNA molecules: heterochromatic localization and role of Dnmt3L. *J. Biol. Chem.* 286(27), 24200–24207 (2011).
- 7 Rajavelu AEA. Function and disruption of DNA methyltransferase 3a cooperative DNA binding and nucleoprotein filament formation. *Nucleic Acids Res.* (2011) (In Press).
- 8 Lister R, Pelizzola M, Dowen RH *et al.* Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature* 462(7271), 315–322 (2009).
- 9 Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for *de novo* methylation and mammalian development. *Cell* 99(3), 247–257 (1999).
- 10 Gowher H, Jeltsch A. Enzymatic properties of recombinant Dnmt3a DNA methyltransferase from mouse: the enzyme modifies DNA in a non-processive manner and also methylates non-CpG sites. *J. Mol. Biol.* 309(5), 1201–1208 (2001).
- 11 Hanson M, Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD. Developmental plasticity and developmental origins of non-communicable disease: theoretical considerations and epigenetic mechanisms. *Prog. Biophys. Mol. Biol.* 106(1), 272–280 (2011).
- 12 Zhang Y, Jurkowska R, Soeroes S *et al.* Chromatin methylation activity of Dnmt3a and Dnmt3a/3L is guided by interaction of the ADD domain with the histone H3 tail. *Nucleic Acids Res.* 38(13), 4246–4253 (2010).
- 13 Dhayalan A, Rajavelu A, Rathert P *et al.* The Dnmt3a PWWP domain reads histone 3 lysine 36 trimethylation and guides DNA methylation. *J. Biol. Chem.* 285(34), 26114–26120 (2010).
- 14 Williamson CM, Ball ST, Dawson C *et al.* Uncoupling antisense-mediated silencing and DNA methylation in the imprinted *Gnas* cluster. *PLoS Genet.* 7(3), e1001347 (2011).
- 15 Myant K, Termanis A, Sundaram AY *et al.* LSH and G9a/GLP complex are required for developmentally programmed DNA methylation. *Genome Res.* 21(1), 83–94 (2011).
- 16 De Vos D, Frederiks F, Terweij M *et al.* Progressive methylation of ageing histones by Dot1 functions as a timer. *EMBO Rep.* 12(9), 956–962 (2011).
- 17 Wossidlo M, Nakamura T, Lepikhov K *et al.* 5-hydroxymethylcytosine in the mammalian zygote is linked with epigenetic reprogramming. *Nat. Commun.* 2, 241 (2011).
- 18 Williams K, Christensen J, Pedersen MT *et al.* TET1 and hydroxymethylcytosine in transcription and DNA methylation fidelity. *Nature* 473(7347), 343–348 (2011).