Epigenetic reprogramming and pericentric heterochromatin remodeling after nuclear transfer as a marker of developmental potential?

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COLLÈGE DE FRANCE
1530

CHAIRE D'EPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

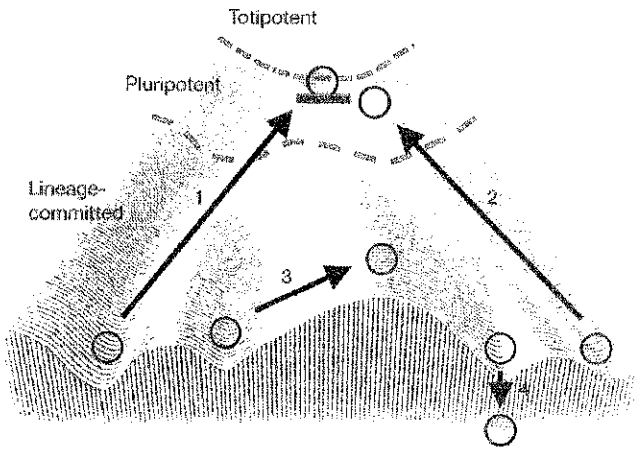
ANNÉE ACADÉMIQUE 2013-2014

EDITH HEARD, PROFESSEUR

REPROGRAMMATIONS DÉVELOPPEMENTALES, INDUITES ET PATHOLOGIQUES"

MONDAY MAY 26TH, 2014

"REPROGRAMMING"



Colloquium on "REPROGRAMMING"

Monday 26th MAY, 2014

"Reprogrammations développementales, induites et pathologiques »

Amphithéâtre Marguerite de Navarre

9.00 am	*Welcome Coffee*
9.30 am	Nicole Le Douarin, *Collège de France, Paris* "From the emergence of the Stem Cell concept to reprogramming of adult differentiated cells"
10.30 am	Helen Blau, *Stanford University, California, USA* "Reprogramming Cell Fate"
11.15 am	*Coffee*
11.45 am	Jacob Hanna, *Weizmann Institute of Science, Israel* "The Epigenetic 'In'stability of the Pluripotent and Somatic Cell States"
12.30 am	*Lunch (speakers only)*
2.00 pm	Azim Surani, *Gurdon Institute, University of Cambridge, UK* "Germline – Specification and epigenetic programming for totipotency and development"
2.45 pm	Nathalie Beaujean, *INRA, Jouy-en-Josas, France* «Epigenetic reprogramming and pericentric heterochromatin remodeling after nuclear transfer as a marker of developmental potential? »
3.30 pm	*Coffee*
4.00 pm	Rob Martienssen, *CSHL, New York, USA* "Germline reprogramming in plants through histone variants and small RNA"
4.45 pm	Rick Livesey, *Gurdon Institute, University of Cambridge, UK* "Human stem cell models of brain development, evolution and disease"
5.30 pm	John Harris, *Institute for Science, Ethics and Innovation, School of Law, University of Manchester, UK* "Multiplex Parenting: IVG and the generations to come"

End 6.15 pm

parental methylomes Cell 153, 737-739
3. Magnusdottir E, Dietmann S, Murakami, Tang S, Gunesdogan U, Lao K, Gottgens B, Surani MA (2013) A tripartite transcription factor network regulates primordial germ cell specification in mice. Nature Cell Biology 15, 908-917
4. Hackett JA, Sengupta,R, Zylicz JJ, Murakami K, Lee C, Down TA, Surani MA (2013) Germline DNA demethylation dynamics and imprint erasure through 5-hydoxymethylcytosine Science, 339, 448-452

Nathalie Beaujean, *INRA, Jouy-en-Josas, France*

« Epigenetic reprogramming and pericentric heterochromatin remodeling after nuclear transfer as a marker of developmental potential? »

Reprogramming by Nuclear Transfer (NT) has caught the interest of many research groups due to the opportunity of testing nuclear potency. Moreover, the opportunity to clone by NT has been achieved in a variety of mammalian species and has potential applications for human health, improvement of agriculture species, protection of exotic and endangered species and advancement of basic biological research (Murphey et al., 2009). On the other hand, the overall efficiency of producing live cloned offspring is quite low. Although many species can now be cloned, most SCNT embryos undergo developmental arrest before or soon after implantation and the success rate of live offspring production remains very low (Wakayama 2007).
During normal development the two very specialized cells, the sperm and the oocyte, undergo profound changes; they lose their characteristic nuclear and chromatin configuration giving way to the establishment of an embryonic chromatin/nuclear organization. It is exactly this distinctive embryonic configuration that should be achieved by the donor nucleus after nuclear transfer in order to sustain proper embryonic genes expression and further development. In this case, the donor cell is forced to setback its differentiated state to an undifferentiated embryonic by reprogramming of its epigenetic memory (Hochedlinger and Jaenisch, 2006).
There are many studies pointing out the different epigenetic constrains seen in NT embryos, such as aberrant DNA methylation patterns as well as abnormal histone modification patterns (Beaujean et al., 2004; Ribeiro-Mason et al., 2012; Pichugin et al., 2010). These results clearly illustrate the heterogeneity of epigenetic alterations found in cloned embryos and new methods have emerged to improve the NT technique: the use of histone deacetylases inhibitors for example that improve nuclear reprogramming by chromatin unfolding (Kishigami et al., 2006 ; Maalouf et al., 2009).
As epigenetic modifications are in close relation to chromatin/nuclear remodeling, the different epigenetic deregulations observed after nuclear transfer could be one of the causes of the abnormal nuclear reprogramming seen in cloned embryos. Indeed, even though there is a great chromatin remodeling imposed by the oocyte reprogramming factors in the donor nucleus, the switch from a "somatic" configuration to an embryonic one is often not well achieved. We for example showed that the percentage of cloned embryos with abnormal heterochromatin redistribution correlates to the proportion of the cloned embryos which failed to develop to blastocyst stage (Maalouf et al., 2009; Yang et al., 2013). Remarkably, we observed improved structural remodeling after transfer with the histone deacetylase inhibitor TSA and full term development improvement (10 times increase) (Maalouf et al., 2009 Lebourhis et al., 2010). Interestingly, the percentage of such abnormalities will depend on the differentiation

status of the nucleus transferred. We indeed observed that ES and iPS cells nuclei undergo better remodeling after NT than somatic nuclei (Maalouf et al., 2009; Liu et al., 2012).
Altogether, we have evidenced a link between the developmental inefficiency of NT embryos and aberrant chromatin reprogramming. Studying NT as a model therefore offers a unique opportunity to understand how the genome and the epigenome have to be reorganized to allow development.
This work is supported by the REVIVE Labex.

Rob Martienssen, *CSHL, New York, USA*

"Germline reprogramming in plants through histone variants and small RNA"

Epigenetic inheritance is more widespread in plants than in mammals, in part because mammals erase epigenetic information by germline reprogramming. We sequenced the methylome of three haploid cell types from developing pollen: the sperm cell, the vegetative cell, and their precursor, the postmeiotic microspore, and found that unlike in mammals the plant germline retains CG and CHG DNA methylation. However, CHH methylation is lost from retrotransposons in microspores and sperm cells and restored by de novo DNA methyltransferase guided by 24 nt small interfering RNA, both in the vegetative nucleus and in the embryo after fertilization. In the vegetative nucleus, CG methylation is lost from targets of DEMETER (DME), REPRESSOR OF SILENCING 1 (ROS1), and their homologs. These targets include imprinted loci and recurrent epialleles that accumulate corresponding small RNA and are premethylated in sperm. Thus genome reprogramming in pollen contributes to epigenetic inheritance, transposon silencing, and imprinting, guided by small RNA. The relative stability of DNA methylation in pollen cell types indicates that loss of DNA methylation does not account for activation of transposons during and immediately following meiosis. Instead, histone modification is a likely candidate. Histone variants have been proposed to act as determinants for the selective deposition of post-translational modifications (PTM) with widespread regulatory functions in eukaryotes. We have found the first example of a histone modifying enzyme that selectively deposits an epigenetic mark on the replication-dependent histone H3 variant H3.1. We solved the crystal structure of the SET domain of the histone H3 lysine 27 (H3K27) methyltransferase ARABIDOPSIS TRITHORAX-RELATED PROTEIN 5 (ATXR5) in ternary complex with a histone H3.1 peptide and S-adenosylhomocysteine (AdoHcy). ATXR5 contains a bipartite catalytic domain characterized by a unique binding pocket that can specifically "reads" alanine 31 of H3.1. Variation at position 31 between H3.1 and the replication-independent variant H3.3 is conserved in plants and animals, and threonine 31 in plant H3.3 is singlehandedly responsible for inhibiting the activity of ATXR5 and its paralog ATXR6 in vitro and in vivo. Our results suggest a simple mechanism for the epigenetic inheritance of the heterochromatic mark H3K27me1 in plants and the protection of H3.3-enriched genes against heterochromatization during DNA replication.

References:

1. Creasey, K.M., Zhai, J., Borges, F., Van Ex, F., Regulski, M., Meyers, B.C., Martienssen, R.A. (2014). miRNAs Trigger Widespread Epigenetically-activated siRNAs from Transposons in Arabidopsis. Nature 2014 Mar 16. doi: