

Décisions épigénétiques et reproduction chez les mammifères

Année de publication : 2019

Maxim Greenberg, Aurélie Teissandier, Marius Walter, Daan Noordermeer, Deborah Bourc'his (2019 Apr 17)

Dynamic enhancer partitioning instructs activation of a growth-related gene during exit from naïve pluripotency.

eLife : [DOI : 10.7554/eLife.44057](https://doi.org/10.7554/eLife.44057)

Résumé

During early mammalian development, the chromatin landscape undergoes profound transitions. The gene-involved in growth control-provides a valuable model to study this window: upon exit from naïve pluripotency and prior to tissue differentiation, it undergoes a switch from a distal to a proximal promoter usage, accompanied by a switch from polycomb to DNA methylation occupancy. Using a mouse embryonic stem cell (ESC) system to mimic this period, we show here that four enhancers contribute to the promoter switch, concomitantly with dynamic changes in chromatin architecture. In ESCs, the locus is partitioned to facilitate enhancer contacts with the distal promoter. Relieving the partition enhances proximal promoter activity, as observed during differentiation or with genetic mutants. Importantly, we show that 3D regulation occurs upstream of the polycomb and DNA methylation pathways. Our study reveals the importance of multi-layered regulatory frameworks to ensure proper spatio-temporal activation of developmentally important genes.

Virginie Carmignac, Julie Barberet, Julian Iranzo, Ronan Quéré, Magali Guilleman, Déborah Bourc'his, Patricia Fauque (2019 Mar 14)

Effects of assisted reproductive technologies on transposon regulation in the mouse pre-implanted embryo.

Human reproduction (Oxford, England) : 612-622 : [DOI : 10.1093/humrep/dez020](https://doi.org/10.1093/humrep/dez020)

Résumé

Do assisted reproductive technologies (ARTs) impact on the expression of transposable elements (TEs) in preimplantation embryos?

Année de publication : 2018

Anne C Ferguson-Smith, Deborah Bourc'his (2018 Oct 23)

The discovery and importance of genomic imprinting.

eLife : [DOI : 10.7554/eLife.42368](https://doi.org/10.7554/eLife.42368)

Résumé

The discovery of genomic imprinting by Davor Solter, Azim Surani and co-workers in the

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mid-1980s has provided a foundation for the study of epigenetic inheritance and the epigenetic control of gene activity and repression, especially during development. It also has shed light on a range of diseases, including both rare genetic disorders and common diseases. This article is being published to celebrate Solter and Surani receiving a 2018 Canada Gairdner International Award « for the discovery of mammalian genomic imprinting that causes parent-of-origin specific gene expression and its consequences for development and disease ».

Raquel Pérez-Palacios, Deborah Bourc'his (2018 Jun 20)

A single-cell chromatin map of human embryos.

Nature cell biology : 742-744 : [DOI : 10.1038/s41556-018-0134-z](https://doi.org/10.1038/s41556-018-0134-z)

Résumé

Année de publication : 2017

C Choux, C Binquet, V Carmignac, C Bruno, C Chapusot, J Barberet, M Lamotte, P Sagot, D Bourc'his, P Fauque (2017 Dec 14)

The epigenetic control of transposable elements and imprinted genes in newborns is affected by the mode of conception: ART versus spontaneous conception without underlying infertility.

Human reproduction (Oxford, England) : 331-340 : [DOI : 10.1093/humrep/dex366](https://doi.org/10.1093/humrep/dex366)

Résumé

Do assisted reproductive technologies alter DNA methylation and/or transcription of transposable elements and imprinted genes in cord blood and placenta?

Aurélie Teissandier, Déborah Bourc'his (2017 Apr 27)

Gene body DNA methylation conspires with H3K36me3 to preclude aberrant transcription.

The EMBO journal : 1471-1473 : [DOI : 10.15252/emj.201796812](https://doi.org/10.15252/emj.201796812)

Résumé

Yara Tarabay, Mayada Achour, Marius Teletin, Tao Ye, Aurélie Teissandier, Manuel Mark, Déborah Bourc'his, Stéphane Viville (2017 Mar 4)

Tex19 paralogs are new members of the piRNA pathway controlling retrotransposon suppression.

Journal of cell science : [DOI : jcs.188763](https://doi.org/10.1242/jcs.188763)

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Résumé

Tex19 genes are mammalian specific and duplicated in Tex19.1 and Tex19.2 in some species, such as the mouse and rat. It has been demonstrated that mutant Tex19.1 males display a variable degree of infertility whereas they all upregulate MMERVK10C transposons in their germ line. In order to study the function of both paralogs in the mouse, we generated and studied double knockout (Tex19DKO) mutant mice. Adult Tex19DKO males exhibited a fully penetrant phenotype, similar to the most severe phenotype observed in single Tex19.1KO mice, with small testes and impaired spermatogenesis, defects in meiotic chromosome synapsis, persistence of DNA double-strand breaks during meiosis, lack of post-meiotic germ cells and upregulation of MMERVK10C expression. The phenotypic similarities with Piwi KO mice prompted us to check and then demonstrate, by immunoprecipitation and GST pulldown followed by mass spectrometry analyses, that TEX19 paralogs interact with PIWI proteins and their VPTEL domain directly binds piRNAs in adult testes. We therefore identified two new members of the postnatal piRNA pathway.

Maxim V C Greenberg, Juliane Glaser, Máté Borsos, Fatima El Marjou, Marius Walter, Aurélie Teissandier, Déborah Bourc'his (2017 Jan 2)

Transient transcription in the early embryo sets an epigenetic state that programs postnatal growth.

Nature genetics : 110-118 : [DOI : 10.1038/ng.3718](https://doi.org/10.1038/ng.3718)

Résumé

The potential for early embryonic events to program epigenetic states that influence adult physiology remains an important question in health and development. Using the imprinted Zdbf2 locus as a paradigm for the early programming of phenotypes, we demonstrate here that chromatin changes that occur in the pluripotent embryo can be dispensable for embryogenesis but instead signal essential regulatory information in the adult. The Liz (long isoform of Zdbf2) transcript is transiently expressed in early embryos and embryonic stem cells (ESCs). This transcription locally promotes de novo DNA methylation upstream of the Zdbf2 promoter, which antagonizes Polycomb-mediated repression of Zdbf2. Strikingly, mouse embryos deficient for Liz develop normally but fail to activate Zdbf2 in the postnatal brain and show indelible growth reduction, implying a crucial role for a Liz-dependent epigenetic switch. This work provides evidence that transcription during an early embryonic timeframe can program a stable epigenetic state with later physiological consequences.

Année de publication : 2016

Joan Barau, Aurélie Teissandier, Natasha Zamudio, Stéphanie Roy, Valérie Nalesso, Yann Héroult, Florian Guillou, Déborah Bourc'his (2016 Nov 19)

The DNA methyltransferase DNMT3C protects male germ cells from transposon activity.

Science (New York, N.Y.) : 909-912

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Résumé

DNA methylation is prevalent in mammalian genomes and plays a central role in the epigenetic control of development. The mammalian DNA methylation machinery is thought to be composed of three DNA methyltransferase enzymes (DNMT1, DNMT3A, and DNMT3B) and one cofactor (DNMT3L). Here, we describe the discovery of Dnmt3C, a de novo DNA methyltransferase gene that evolved via a duplication of Dnmt3B in rodent genomes and was previously annotated as a pseudogene. We show that DNMT3C is the enzyme responsible for methylating the promoters of evolutionarily young retrotransposons in the male germ line and that this specialized activity is required for mouse fertility. DNMT3C reveals the plasticity of the mammalian DNA methylation system and expands the scope of the mechanisms involved in the epigenetic control of retrotransposons.

Marius Walter, Aurélie Teissandier, Raquel Pérez-Palacios, Déborah Bourc'his (2016 Jan 27)

An epigenetic switch ensures transposon repression upon dynamic loss of DNA methylation in embryonic stem cells.

eLife : [DOI : 10.7554/eLife.11418](https://doi.org/10.7554/eLife.11418)

Résumé

DNA methylation is extensively remodeled during mammalian gametogenesis and embryogenesis. Most transposons become hypomethylated, raising the question of their regulation in the absence of DNA methylation. To reproduce a rapid and extensive demethylation, we subjected mouse ES cells to chemically defined hypomethylating culture conditions. Surprisingly, we observed two phases of transposon regulation. After an initial burst of de-repression, various transposon families were efficiently re-silenced. This was accompanied by a reconfiguration of the repressive chromatin landscape: while H3K9me3 was stable, H3K9me2 globally disappeared and H3K27me3 accumulated at transposons. Interestingly, we observed that H3K9me3 and H3K27me3 occupy different transposon families or different territories within the same family, defining three functional categories of adaptive chromatin responses to DNA methylation loss. Our work highlights that H3K9me3 and, most importantly, polycomb-mediated H3K27me3 chromatin pathways can secure the control of a large spectrum of transposons in periods of intense DNA methylation change, ensuring longstanding genome stability.

Année de publication : 2015

Hung-Fu Liao, Chu-Fan Mo, Shinn-Chih Wu, Dai-Han Cheng, Chih-Yun Yu, Kai-Wei Chang, Tzu-Hao Kao, Chia-Wei Lu, Marina Pinskaya, Antonin Morillon, Shih-Shun Lin, Winston T K Cheng, Déborah Bourc'his, Timothy Bestor, Li-Ying Sung, Shau-Ping Lin (2015 Jul 11)

Dnmt3l-knockout donor cells improve somatic cell nuclear transfer reprogramming efficiency.

Reproduction (Cambridge, England) : 245-56 : [DOI : 10.1530/REP-15-0031](https://doi.org/10.1530/REP-15-0031)

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Résumé

Nuclear transfer (NT) is a technique used to investigate the development and reprogramming potential of a single cell. DNA methyltransferase-3-like, which has been characterized as a repressive transcriptional regulator, is expressed in naturally fertilized egg and morula/blastocyst at pre-implantation stages. In this study, we demonstrate that the use of Dnmt3l-knockout (Dnmt3l-KO) donor cells in combination with Trichostatin A treatment improved the developmental efficiency and quality of the cloned embryos. Compared with the WT group, Dnmt3l-KO donor cell-derived cloned embryos exhibited increased cell numbers as well as restricted OCT4 expression in the inner cell mass (ICM) and silencing of transposable elements at the blastocyst stage. In addition, our results indicate that zygotic Dnmt3l is dispensable for cloned embryo development at pre-implantation stages. In Dnmt3l-KO mouse embryonic fibroblasts, we observed reduced nuclear localization of HDAC1, increased levels of the active histone mark H3K27ac and decreased accumulation of the repressive histone marks H3K27me3 and H3K9me3, suggesting that Dnmt3l-KO donor cells may offer a more permissive epigenetic state that is beneficial for NT reprogramming.

Natasha Zamudio, Joan Barau, Aurélie Teissandier, Marius Walter, Maté Borsos, Nicolas Servant, Déborah Bourc'his (2015 Jun 26)

DNA methylation restrains transposons from adopting a chromatin signature permissive for meiotic recombination.

Genes & development : 1256-70 : [DOI : 10.1101/gad.257840.114](https://doi.org/10.1101/gad.257840.114)

Résumé

DNA methylation is essential for protecting the mammalian germline against transposons. When DNA methylation-based transposon control is defective, meiotic chromosome pairing is consistently impaired during spermatogenesis: How and why meiosis is vulnerable to transposon activity is unknown. Using two DNA methylation-deficient backgrounds, the Dnmt3L and Miwi2 mutant mice, we reveal that DNA methylation is largely dispensable for silencing transposons before meiosis onset. After this, it becomes crucial to back up to a developmentally programmed H3K9me2 loss. Massive retrotransposition does not occur following transposon derepression, but the meiotic chromatin landscape is profoundly affected. Indeed, H3K4me3 marks gained over transcriptionally active transposons correlate with formation of SPO11-dependent double-strand breaks and recruitment of the DMC1 repair enzyme in Dnmt3L(-/-) meiotic cells, whereas these features are normally exclusive to meiotic recombination hot spots. Here, we demonstrate that DNA methylation restrains transposons from adopting chromatin characteristics amenable to meiotic recombination, which we propose prevents the occurrence of erratic chromosomal events.

Maxim Vc Greenberg, Déborah Bourc'his (2015 May 15)

Cultural relativism: maintenance of genomic imprints in pluripotent stem cell culture systems.

Current opinion in genetics & development : 42-9 : [DOI : 10.1016/j.gde.2015.04.005](https://doi.org/10.1016/j.gde.2015.04.005)

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Résumé

Pluripotent stem cells (PSCs) in culture have become a widely used model for studying events occurring during mammalian development; they also present an exciting avenue for therapeutics. However, compared to their *in vivo* counterparts, cultured PSC derivatives have unique properties, and it is well established that their epigenome is sensitive to medium composition. Here we review the specific effects on genomic imprints in various PSC types and culture systems. Imprinted gene regulation is developmentally important, and imprinting defects have been associated with several human diseases. Therefore, imprint abnormalities in PSCs may have considerable consequences for downstream applications.

Céline Bruno, Virginie Carmignac, Irène Netchine, Cécile Choux, Yannis Duffourd, Laurence Faivre, Christel Thauvin-Robinet, Yves Le Bouc, Paul Sagot, Déborah Bourc'his, Patricia Fauque (2015 Mar 5)

Germline correction of an epimutation related to Silver-Russell syndrome.

Human molecular genetics : 3314-21 : [DOI : 10.1093/hmg/ddv079](https://doi.org/10.1093/hmg/ddv079)

Résumé

Like genetic mutations, DNA methylation anomalies or epimutations can disrupt gene expression and lead to human diseases. However, unlike genetic mutations, epimutations can in theory be reverted through developmental epigenetic reprogramming, which should limit their transmission across generations. Following the request for a parental project of a patient diagnosed with Silver-Russell syndrome (SRS), and the availability of both somatic and spermatozoa DNA from the proband and his father, we had the exceptional opportunity to evaluate the question of inheritance of an epimutation. We provide here for the first time evidence for efficient reversion of a constitutive epimutation in the spermatozoa of an SRS patient, which has important implication for genetic counseling.

Année de publication : 2014

William A Pastor, Hume Stroud, Kevin Nee, Wanlu Liu, Dubravka Pezic, Sergei Manakov, Serena A Lee, Guillaume Moissiard, Natasha Zamudio, Déborah Bourc'his, Alexei A Aravin, Amander T Clark, Steven E Jacobsen (2014 Dec 16)

MORC1 represses transposable elements in the mouse male germline.

Nature communications : 5795 : [DOI : 10.1038/ncomms6795](https://doi.org/10.1038/ncomms6795)

Résumé

The Microorchidia (Morc) family of GHKL ATPases are present in a wide variety of prokaryotic and eukaryotic organisms but are of largely unknown function. Genetic screens in *Arabidopsis thaliana* have identified Morc genes as important repressors of transposons and other DNA-methylated and silent genes. MORC1-deficient mice were previously found to

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display male-specific germ cell loss and infertility. Here we show that MORC1 is responsible for transposon repression in the male germline in a pattern that is similar to that observed for germ cells deficient for the DNA methyltransferase homologue DNMT3L. Morc1 mutants show highly localized defects in the establishment of DNA methylation at specific classes of transposons, and this is associated with failed transposon silencing at these sites. Our results identify MORC1 as an important new regulator of the epigenetic landscape of male germ cells during the period of global de novo methylation.