Year of publication 2013

Rachel Duffié, Déborah Bourc'his (2013 Apr 17)

**Parental epigenetic asymmetry in mammals.**

*Current topics in developmental biology* : 293-328 : [DOI : 10.1016/B978-0-12-416027-9.00009-7]

**Summary**

The early mammalian embryo is marked by genome-wide parental epigenetic asymmetries, which are directly inherited from the sperm and the oocyte, but are also amplified a few hours after fertilization. The yin-yang of these complementary parental programs is essential for proper development, as uniparental embryos are not viable. The majority of these parental asymmetries are erased, as the embryonic genome assumes its own chromatin signature toward pluripotency and then differentiation, reducing the risk for haploinsufficiency. At a few loci, however, parent-of-origin information persists through development, via maintenance and protective complexes. In this review, we discuss the parental asymmetries that are inherited from the gametes, the forces involved in their elimination, reinforcement or protection, and how this influences the embryonic program. We highlight the gradual loss of all parental asymmetries occurring throughout development, except at imprinted loci, which maintain distinct parent-of-origin chromatin and transcriptional characteristics for life. A deeper understanding of the nongenetic contributions of each germline is important to provide insight into the origin of non-Mendelian inheritance of phenotypic traits, as well as the risk of incompatibilities between parental genomes.

Mounia Guenatri, Rachel Duffié, Julian Iranzo, Patricia Fauque, Déborah Bourc'his (2013 Jan 8)

**Plasticity in Dnmt3L-dependent and -independent modes of de novo methylation in the developing mouse embryo.**


**Summary**

A stimulatory DNA methyltransferase co-factor, Dnmt3L, has evolved in mammals to assist the process of de novo methylation, as genetically demonstrated in the germline. The function of Dnmt3L in the early embryo remains unresolved. By combining developmental and genetic approaches, we find that mouse embryos begin development with a maternal store of Dnmt3L, which is rapidly degraded and does not participate in embryonic de novo methylation. A zygotic-specific promoter of Dnmt3l is activated following gametic methylation loss and the potential recruitment of pluripotency factors just before implantation. Importantly, we find that zygotic Dnmt3L deficiency slows down the rate of de novo methylation in the embryo by affecting methylation density at some, but not all, genomic sequences. Dnmt3L is not strictly required, however, as methylation patterns are eventually established in its absence, in the context of increased Dnmt3A protein availability. This study proves that the postimplantation embryo is more plastic than the germline in terms of DNA methylation mechanistic choices and, importantly, that de novo methylation can be achieved in vivo without Dnmt3L.
Year of publication 2012

Isabel Iglesias-Platas, Alex Martin-Trujillo, Davide Cirillo, Franck Court, Amy Guillaumet-Adkins, Cristina Camprubi, Deborah Bourc'his, Kenichiro Hata, Robert Feil, Gian Tartaglia, Philippe Arnaud, David Monk (2012 Jun 23)

Characterization of novel paternal ncRNAs at the Plagl1 locus, including Hymai, predicted to interact with regulators of active chromatin.

PloS one : e38907 : DOI : 10.1371/journal.pone.0038907

Summary

Genomic imprinting is a complex epigenetic mechanism of transcriptional control that utilizes DNA methylation and histone modifications to bring about parent-of-origin specific monoallelic expression in mammals. Genes subject to imprinting are often organised in clusters associated with large non-coding RNAs (ncRNAs), some of which have cis-regulatory functions. Here we have undertaken a detailed allelic expression analysis of an imprinted domain on mouse proximal chromosome 10 comprising the paternally expressed Plagl1 gene. We identified three novel Plagl1 transcripts, only one of which contains protein-coding exons. In addition, we characterised two unspliced ncRNAs, Hymai, the mouse orthologue of HYMAI, and Plagl1it (Plagl1 intronic transcript), a transcript located in intron 5 of Plagl1. Imprinted expression of these novel ncRNAs requires DNMT3L-mediated maternal DNA methylation, which is also indispensable for establishing the correct chromatin profile at the Plagl1 DMR. Significantly, the two ncRNAs are retained in the nucleus, consistent with a potential regulatory function at the imprinted domain. Analysis with catRAPID, a protein-ncRNA association prediction algorithm, suggests that Hymai and Plagl1it RNAs both have potentially high affinity for Trithorax chromatin regulators. The two ncRNAs could therefore help to protect the paternal allele from DNA methylation by attracting Trithorax proteins that mediate H3 lysine-4 methylation.


Protection against de novo methylation is instrumental in maintaining parent-of-origin methylation inherited from the gametes.

Molecular cell : 909-20 : DOI : 10.1016/j.molcel.2012.07.010

Summary

Identifying loci with parental differences in DNA methylation is key to unraveling parent-of-origin phenotypes. By conducting a MeDIP-Seq screen in maternal-methylation free postimplantation mouse embryos (Dnmt3L-/+), we demonstrate that maternal-specific methylation exists very scarcely at midgestation. We reveal two forms of oocyte-specific methylation inheritance: limited to preimplantation, or with longer duration, i.e. maternally imprinted loci. Transient and imprinted maternal germline DMRs (gDMRs) are indistinguishable in gametes and preimplantation embryos, however, de novo methylation of
paternal alleles at implantation delineates their fates and acts as a major leveling factor of parent-inherited differences. We characterize two new imprinted gDMRs, at the Cdh15 and AK008011 loci, with tissue-specific imprinting loss, again by paternal methylation gain. Protection against demethylation after fertilization has been emphasized as instrumental in maintaining parent-of-origin methylation inherited from the gametes. Here we provide evidence that protection against de novo methylation acts as an equal major pivot, at implantation and throughout life.