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Review

Germline-derived DNA methylation and early embryo epigenetic reprogramming: The selected survival of imprints☆

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ABSTRACT

DNA methylation is an essential epigenetic mechanism involved in many essential cellular processes. During development epigenetic reprograming takes place during gametogenesis and then again in the pre-implantation embryo. These two reprograming windows ensure genome-wide removal of methylation in the primordial germ cells so that sex-specific signatures can be acquired in the sperm and oocyte. Following fertilization the majority of this epigenetic information is erased to give the developing embryo an epigenetic profile coherent with pluripotency. It is estimated that ~65% of the genome is differentially methylated between the gametes, however following embryonic reprogramming only parent-of-origin methylation at known imprinted loci remains. This suggests that *trans*-acting factors such as Zfp57 can discriminate imprinted differentially methylated regions (DMRs) from the thousands of CpG rich regions that are differentially marked in the gametes. Recently transient imprinted DMRs have been identified suggesting that these loci are also protected from pre-implantation reprograming but succumb to *de novo* remethylation at the implantation stage. This highlights that "ubiquitous" imprinted loci are also resilient to gaining methylation by protecting their unmethylated alleles. In this review I examine the processes involved in epigenetic reprograming and the mechanisms that ensure allelic methylation at imprinted loci is retained throughout the life of the organism, discussing the critical differences between mouse and humans.

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Abbreviations: 5mC, 5-methylcytosine; ES cells, embryonic stem cells; SAM, S-adenosyl-methionine; Dnmt, DNA methyltransferase; Uhrf1, Ubiquitin-like, containing PHD and RING finger domains 1; H3K, Histone H3 lysine; Cfp1, CXXC finger protein 1; Ezh2, enhancer of zeste homolog 2; LINE, long interspersed elements; ncRNA, non-coding RNA; Xic, X chromosome inactivation center; Xist, X inactive specific transcript; Tsix, Xist antisense transcript; XACT, Xactive specific transcript; DMR, differentially methylated region; PGC, primordial germ cells; Aid, activation-induced cytidine deaminase; TET, ten-eleven translocation; TDG, thymine DNA glycosylase; 5hmC, 5-hydroxymethylcytosine; RRBS, reduced representations bisulphite sequencing; NLRP, NLR family pyrin domain containing protein; YY1, ying yang transcription factor; DPPA3, developmental pluripotency associated 3; TRIM28, tripartite motif containing 28; ZFP57, zinc finger protein 57; CTCF, CCTC-binding factor.

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1. Introduction

During the development of higher organisms, cells undertake fate decisions whether to terminally differentiate based on epigenetic signals that are required to reinforce cell-specific transcriptional profiles. These epigenetic changes ensure cell specification and are stable and heritable through mitosis, ensuring propagation of lineage-specific gene expression. These heavily enforced epigenetic signals, of which DNA methylation and chromatin modifications are the most studied, pose a major obstacle for sexual reproduction, though the union of highly specialized gametes. In preparation for reproduction, the epigenomes must undergo erasure of the somatic cell signatures in the primordial germ cells, establish germ cell-specific epigenetic signatures whilst initiating meiosis, and finally, undergo post-fertilization reprograming to ensure a totipotent state necessary for embryonic development.

Although much of our knowledge of epigenetic reprogramming in embryos and germ cells have originated from observations in mice, recent studies have suggested that there are subtle difference in human germline epigenetic processes. Throughout this review, I will shed insight into the molecular difference between species, and give an up-to-date snapshot of the current understanding of the role of germline methylation differences, focusing on the example of genomic imprinting.

1.1. DNA methylation – the 5th base

The methylation of the fifth carbon of the cytosine ring (5mC) is often referred to as the fifth base of the DNA code. DNA methylation is vital for mammalian development and represents the best-characterized epigenetic modifications, playing important roles in a variety of cellular processes including controlling gene expression, repression of retrotransposons, maintenance of genome stability, X chromosome dosage compensation and the coordinated regulation of imprinted genes.

DNA methylation is most predominately observed in a symmetrical CpG dinucleotide and consequently our genomes present with under-presentation of CpGs owing to the spontaneous deamination of 5mC to thymidines (T). Globally the methylated CpG spares landscape is punctuated with CpG islands, intervals of DNA characterized by high G + C composition that are frequently devoid of methylation (Weber et al., 2007). Approximately 70% of annotated gene promoters are associated with CpG islands, making them the most common type of promoter in mammalian genomes (Illingworth et al., 2010). DNA methylation has also been observed in non-CpG contexts (where H = A, C or T), specifically in oocytes, embryonic stem (ES) cells and specific cell types of the brain, although its function remains unclear (Lister et al., 2009, 2013; Ichiyanagi et al., 2013).

1.2. The *de novo* methylation machinery

The DNA methyltransferases catalyze the transfer of a methyl group from the methyl donor S-adenosyl-methionine (SAM) to the fifth position of cytosines residues. New DNA methylation patterns are initially established by the *de novo* DNA methyltransferases Dnmt3a and Dnmt3b. In mouse Dnmt3a is predominantly expressed in oocytes and early embryos and is responsible for establishing methylation at imprinted control regions in both male and female gametes. Dnmt3b is expressed at later stages of preimplantation embryos development, following the zygotic gene activation and is responsible for remethylation following embryonic reprogramming. Targeted deletions of *Dnmt3b* and *Dnmt3a* are both lethal; lack of *Dnmt3b* results in embryonic lethality, whereas homozygous *Dnmt3a* knockout mice die one month after birth (Okano et al., 1999). Combined genetic deletions result in an earlier embryonic lethality, indicating partial redundancy of these two enzymes during development. Their respective roles in establishing germline methylation are confirmed using conditional germline deletions, in which the genes were preserved in somatic tissues (Kaneda et al., 2004). Offspring from *Dnmt3a* conditional mutant females die *in utero*, whereas *Dnmt3b* conditional mutants show no apparent phenotype. A third DNA methyltransferase shares homology with Dnmt3. Dnmt3l possesses a plant homeodomain (PHD)-like motif but lacks the N-terminal catalytic domain and appears to have no enzymatic activity. Instead, Dnmt3l cooperates with Dnmt3a and Dnmt3b to establish maternal methylation in the oocyte and is necessary for spermatogenesis (Bourc'his et al., 2001; Bourc'his and Bestor, 2004). Interestingly the phenotype of *Dnmt3a* conditional germline mutant is indistinguishable from that of *Dnmt3l* knockout mice, indicating that both Dnmt3a and Dnmt3l are required for methylation of most imprinted loci in germ cells.

1.2.1. Methylation maintenance machinery

The pattern of DNA methylation is faithfully maintained during DNA replication by the maintenance methyltransferase Dnmt1, which shows high affinity for hemimethylated CpGs. The expression of *Dnmt1* is activated transcription factors most abundant during S-phase (Kishikawa et al., 2003), and is recruited to replication foci *via* its physical interaction with the ubiquitin-like plant homeodomain and RING finger domain 1 (Uhrf1) protein, where it restores hemimethylated DNA to a fully methylated state (Bostick et al., 2007; Sharif et al., 2007). Two isoforms of *Dnmt1* have been described in mouse and orthologues have been identified in humans; the ubiquitously expressed somatic form (*Dnmt1s*) and

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