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Environmental effects on chromatin repression at imprinted genes and endogenous retroviruses

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Environmental factors can perturb epigenetic regulation. In mammals, most studies have focused on repressive DNA methylation. Two attractive model systems to monitor environmentally triggered drifts in DNA methylation are genomic imprinting and endogenous retroviruses (ERVs), particularly intracisternal-A particles (IAPs). These systems show mechanistic similarities in their repressive chromatin organization, which in somatic cells is comparable between the DNA-methylated alleles of imprinted differentially methylated regions (DMRs) and repressed ERVs. Here, we present how during development, nutrition and chemical components can perturb DNA methylation at imprinted genes and ERVs, and discuss the still poorly understood underlying mechanisms.

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Introduction

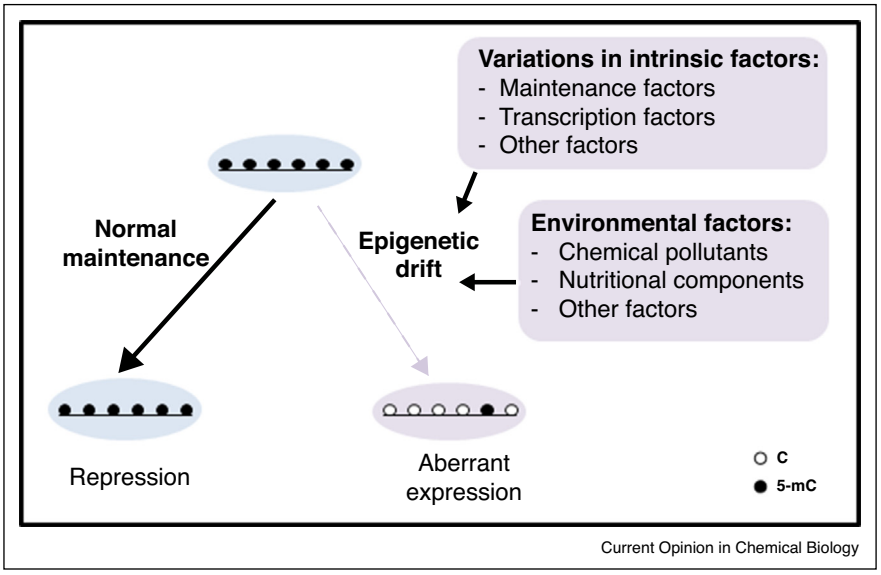
Many sequences in the mammalian genome are repressed by methylation at the 5-position of cytosines (5-mC) [1]. Though generally stable, 5-mC-associated chromatin repression may become perturbed for different reasons. Such 'epigenetic drift' (Figure 1) can be linked to intrinsic factors, or can be triggered by external cues such as dietary composition and chemical pollutants [2].

Besides other functions, 5-mC contributes to the repression of transposable elements [1]. These are DNA sequence elements that can change their position in the genome. Collectively, the different transposable elements constitute about half of the mammalian genome [3]. Of particular interest are endogenous retroviruses (ERVs), which are retrovirus-like genetic elements that have undergone considerable expansion in mammals. Amongst the active ERVs (still able to retrotranspose) in rodents are the 'Intracisternal-A-particles' (IAPs) of which ~4000 full-length copies are present across the genome [4•]. This class-II ERV [3], encoding virus-like particles, and other long terminal repeat (LTR) retrotransposons, influence gene expression and phenotype, particularly in the placenta where they are less tightly repressed [5–7]. Nevertheless, it is essential to keep ERVs globally repressed to prevent deleterious retrotransposition [6–8].

In mouse embryonic stem cells (ESCs), besides at IAPs [9], 5-mC plays a minor role only in ERV repression [10]. Krüppel-Associated Box (KRAB)-domain zinc-finger proteins (ZFPs) bind specific sequences at ERVs and recruit the platform protein Trim28 (also called Kap1) to the chromatin [8,11,12]. This facilitates recruitment of lysine methyltransferase (KMT) Setdb1 (also called Eset, Kmt1e), leading to histone H3-lysine-9 trimethylation (H3K9me3), which is important for repression of class I and II ERVs [10,13]. Setdb1 also contributes to the somatic maintenance of DNA methylation, particularly in embryonic cells [8,13–15]. Heterochromatin protein-1 (Hp1α and Hp1β) is recruited through recognition of both H3K9me3 and Trim28 and locally compacts the chromatin, but is not essential for ERV repression in embryonic cells [12,16]. DNA methylation is recognized by methyl CpG binding domain (MBD) proteins that, in turn, recruit additional chromatin repressors, including histone deacetylases (HDACs) [14]. Lastly, the ATP-dependent helicase/chromatin remodeler Atrx ('Alpha-thalassemia X-linked') and its interacting histone chaperone Daxx ('death domain-associated protein') mediate deposition of variant histone H3.3, which facilitates Setdb1-mediated H3K9me3 and the maintenance and spreading of heterochromatin [17•,18•] (Figure 2a). Depending on the cell-type and the ERV sequence context, these diverse and interlinked mechanisms contribute to different extents to the chromatin repression [14].

Genomic imprinting is an essential, epigenetic phenomenon in mammals that brings about mono-allelic gene expression at >100 genes, entirely dependent on the parental origin of the allele ('gene copy') [19,20]. Imprinted genes are organized in evolutionarily conserved clusters and their allelic expression is controlled by 'imprinting control regions' (ICRs) [21], which are essential *cis*-regulatory sequence elements of several

Figure 1



Somatic maintenance and environmental perturbation of repressive DNA methylation. 5-mC (black circles)-associated chromatin repression is somatically maintained at many regions in the genome, including at imprinted loci and ERVs. Stochastic variations in maintenance factors, however, may give rise to loss of DNA methylation (white circles) during development. Environmental factors can disrupt the maintenance process as well, through diverse mechanisms, often with long-term consequences for gene expression and phenotype [2].

kilobases that are marked by 5-mC on one of the two parental alleles only. These allelic 'imprints' are somatically maintained throughout development [21]. The mechanisms involved in this stable maintenance process (Figure 3a) show mechanistic similarities to the maintenance of ERV silencing [12], and it has therefore been hypothesized that the evolution of imprinting is linked to host defense against retrotransposons [22–24]. In embryonic cells, the allelic DNA methylation at ICRs is linked to Setdb1-mediated H3K9me3, and to H4 lysine-20 trimethylation (H4K20me3) mediated by the KMT Suv4-20h (also called Kmt5c) [25,26]. Similarly as at ERVs, there is recruitment of MBD proteins and Hp1 (mostly Hp1γ), Atrx/Daxx mediated H3.3 and an essential involvement of a KRAB-domain ZFP (*i.e.*, Zfp57) that brings Trim28 (and Setdb1) to the chromatin [26,27•,28,29]. Zfp57, Trim28, Setdb1, Atrx and other recruited proteins contribute to different extents to the chromatin repression at ICRs [13,21,26,27•,28,29].

Mouse models to monitor environmental effects on chromatin repression

Imprinted genes and IAP insertions into developmental genes provide powerful tools to monitor environmental effects on 5-mC-linked chromatin repression. Studies on imprinted genes are biologically relevant as well, because of their essential roles in development, metabolism and behavior [20]. An experimental advantage of imprinting is that repressed (DNA-methylated) and active (unmethylated) alleles can be directly compared within the same cells, which allows detection of even minor epigenetic shifts (Figure 3b).

Many genetic mutants in mice arose through IAP retrotransposition [6,30]. The best-studied is *Agouti viable yellow* (A^{VY}), a mutation that arose through IAP insertion upstream of the coat color gene *Agouti* [31]. This IAP comprises an LTR that, when hypo-methylated, gives aberrant, widespread transcription of *Agouti*, which induces yellow coat color and obesity (Figure 2b). A^{VY} is called 'metastable' [31] because its expression states are rather labile and variable between offspring, depending on the methylation status of its IAP (Figure 2b). By careful screening of coat color patterns the model provides a sensitive readout of how environmental factors influence IAP methylation and repression [32]. A similar metastable mouse mutant is *Axin-fused* ($Axin^{FU}$), where an IAP inserted into the *Wnt* signaling pathway gene *Axin*. Also here, the phenotype associated with loss of IAP methylation ('a kinked tail') is apparent in variable fractions of the offspring [33].

Diet and chemical pollutants influence chromatin repression at ERVs

Female A^{VY} mice, when given a standard diet during pregnancy, produce a mixture of pseudo-agouti ('brown'), mottled ('mixture of brown and yellow patches') and yellow offspring [32] (Figure 2b). When females were given additional folate, or other components of the methionine mono-carbon cycle that enhance the availability of