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Review

Chromatin mechanisms in the developmental control of imprinted gene expression☆

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ABSTRACT

Hundreds of protein-coding genes and regulatory non-coding RNAs (ncRNAs) are subject to genomic imprinting. The mono-allelic DNA methylation marks that control imprinted gene expression are somatically maintained throughout development, and this process is linked to specific chromatin features. Yet, at many imprinted genes, the mono-allelic expression is lineage or tissue-specific. Recent studies provide mechanistic insights into the developmentally-restricted action of the 'imprinting control regions' (ICRs). At several imprinted domains, the ICR expresses a long ncRNA that mediates chromatin repression *in cis* (and probably *in trans* as well). ICRs at other imprinted domains mediate higher-order chromatin structuration that enhances, or prevents, transcription of close-by genes. Here, we present how chromatin and ncRNAs contribute to developmental control of imprinted gene expression and discuss implications for disease. This article is part of a Directed Issue entitled: Epigenetics dynamics in development and disease.

Contents

1. Epigenetic control of mammalian genomic imprinting

Epigenetic regulation contributes to development and homeostasis by initiating and maintaining stable patterns of gene expression (Jaenisch and Bird, 2003). During mammalian development, different epigenetic phenomena control transcription levels by conferring mono-allelic expression of some genes. This includes the process of X chromosome inactivation in females and genomic imprinting (Lee and Bartolomei, 2013), a regulatory mechanism

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that brings about mono-allelic gene expression depending on the parental origin of the gene (Ferguson-Smith, 2011). Some imprinted genes are expressed from the maternally inherited allele only (and repressed on the paternal chromosome), whereas others are expressed uniquely from the paternal chromosome. More than hundred protein-coding genes are imprinted in humans and mice (Williamson et al., 2013; Morison et al., 2005). These play diverse roles in development and growth, and contribute to physiology and behaviour (Peters, 2014). It has become apparent that hundreds of regulatory non-coding RNAs (ncRNAs), including microRNAs, snoRNAs and long ncRNAs, are controlled by genomic imprinting as well (Girardot et al., 2012; Pauler et al., 2012). The biological functions of these imprinted ncRNAs remain less well understood. This review highlights the importance of chromatin and imprinted ncRNAs in the developmental control of imprinted gene expression.

Imprinted genes are organised in clusters, forming chromosomal domains of tens of kilobases to several megabases in size (Kelsey and Feil, 2013). The imprinted expression of the genes within each of these domains is controlled by an 'imprinting control region' (ICR). ICRs are essential regulatory DNA elements, which are rich in CpG dinucleotides, and are marked by germline-derived DNA methylation on one of the two parental alleles. ICRs are comparable between each-other in that they all carry parent-of-origin specific DNA methylation, which is maintained throughout development (Kota and Feil, 2010; Smallwood and Kelsey, 2012). This somatic maintenance process involves, besides the 5-methylcytosine (5mC) methylation itself, various protein factors and covalent histone modifications (Kacem and Feil, 2009; Kelsey and Feil, 2013). The way the differentially methylated ICRs bring about the imprinted gene expression at nearby genes differs between domains. At several domains the imprinted expression is tissue-specific (Peters, 2014). The way in which ICRs mediate imprinted expression involves covalent chromatin modifications and higher order chromatin structuration. At some imprinted loci, interestingly, the tissue-specificity is linked to the action of imprinted long ncRNAs (lncRNAs). These novel insights are presented and discussed below.

2. Chromatin and the control of DNA methylation imprints

2.1. Acquisition of DNA methylation imprints

The specificity of the methylation imprints at ICRs is conferred by their establishment in either the female or the male germline. The majority of ICRs are methylated on the maternally-inherited allele, carrying a methylation mark acquired during the final stages of oogenesis. Only three ICRs are 'paternally methylated' in mice and humans, with the allelic DNA methylation originating from sperm, with imprint acquisition occurring during the fetal stages of spermatogenesis (Kota and Feil, 2010). Besides the requirement of the *de novo* DNA methyltransferase DNMT3A, and that of a non-catalytically active partner protein, called DNMT3-like (DNMT3L), imprint acquisition is not fully understood (Kelsey and Feil, 2013; Kota and Feil, 2010). What determines that the DNMT3A/DNMT3L protein complex is brought to one set of ICR regions in one germline, and to another, in the other germline? Insights into this key question have emerged. Transcription through the ICR regions seems essential to the process (Chotalia et al., 2009; Henckel et al., 2012). The modification status of the chromatin associated with ICRs is important as well —particularly histone H3 methylation at lysine-4 — and determines whether the *de novo* methylation machinery has access or not to its target regions (Ciccone et al., 2009; Henckel et al., 2012; Ooi et al., 2007). Several recent reviews discuss these novel insights into imprint acquisition (Duffie and Bourc'his, 2013; Kelsey and Feil, 2013; Kota and Feil, 2010).

2.2. Somatic maintenance of the methylated allele

Here, we are interested in another determinant of imprinting specificity: the somatic maintenance of the differential DNA methylation status of ICRs. Genome-wide methylation studies have revealed that more than thousand promoter/CpG island regions become methylated in either the male or the female germline (Kobayashi et al., 2012; Smallwood et al., 2011). The differential methylation is maintained during pre-implantation development at some of these regions only, and these include all the known ICRs (Duffie and Bourc'his, 2013; Reik et al., 2001). This exceptional epigenetic maintenance of ICRs is linked to differential patterns of histone lysine and arginine methylation between the parental chromosomes, and several of the responsible histone modifying enzymes have been identified (Kelsey and Feil, 2013). Particularly, chromatin associated with the DNA-methylated alleles of ICRs is consistently marked by histone H3 lysine-9 trimethylation (H3K9me3), H3 lysine-64 tri-methylation (H3K64me3), H4 lysine-20 trimethylation (H4K20me3) and H4 arginine-3 symmetrical dimethylation (H4R3me2s), and is bound by the heterochromatin protein-1 gamma (HP1γ) (Delaval et al., 2007; Girardot et al., 2014; Pannetier et al., 2008). To which extent these 'repressive chromatin' features, similar to those at constitutive heterochromatin, contribute to the maintenance of the DNA methylation is not clear. Studies on mouse embryonic stem cells have revealed minor losses of DNA methylation due to depletion of specific lysine methyltransferases (KMTs), including the H3-lysine-9 enzymes G9a and ESET/SETDB1 (Girardot et al., 2014; Leung et al., 2014; Quenneville et al., 2011). It is unclear whether these findings reflect the *in vivo* situation in the embryo. Absence of G9a in the embryo does not result in loss of DNA methylation at ICRs (Wagschal et al., 2008; Xin et al., 2003).

DNMT1 is essential for the embryonic maintenance of the DNA methylation imprints (Hirasawa et al., 2008). Studies on imprinting-related diseases in humans (Hirasawa and Feil, 2010) have pinpointed proteins that contribute to the imprint maintenance by DNMT1, particularly in the early embryo (Table 1). One of these is the KRAB-domain zinc-finger protein ZFP57 (Li et al., 2008), a protein which recruits KAP1 (also called TRIM28, or TIF1B), a platform protein which, in turn, mediates recruitment of histone modifying enzymes, including the H3-lysine-9 specific ESET/SETDB1 (Hirasawa and Feil, 2008). ZFP57 binds to methylated DNA sequences through recognition of a specific sequence motif ('TGCCGC'), found at many ICRs and at some other differentially methylated regions (DMRs) as well (Quenneville et al., 2011). In humans, *ZFP57* mutations are associated with 'transient neonatal diabetes mellitus' (TNDM). In these patients, the imprinting disorder (ID) is caused by the resulting loss of DNA methylation at the *PLAGL1* gene (Mackay et al., 2008). In some TNDM patients with heterozygous inactivating *ZFP57* mutations, DNA methylation loss affects other ICRs as well. Mouse studies have confirmed that ZFP57 is essential for embryonic imprint maintenance at multiple ICRs (Quenneville et al., 2011).

The first embryonic cell divisions are critical for imprint maintenance and several maternal (*i.e.*, oocyte derived) proteins have been shown to be involved. One of these is DPPA3 (also called Stella or PGC7), a protein present at high levels in oocytes that persists in the early embryo. This chromatin-associated protein contributes to the maintenance of DNA methylation on the maternal set of chromosomes, including at several of the maternal ICRs (Nakamura et al., 2007). DPPA3 also contributes to the early-embryonic maintenance of methylation at two of the paternal ICRs. DPPA3 protects against DNA demethylation by inhibiting the conversion of 5mC to 5-hydroxymethyl-cytosine (5hmC) in the zygote (Wossidlo et al., 2011). How DPPA3 is targeted to specific loci is not clear, but this protein recognizes and binds to H3 lysine-9 dimethylation

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