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Review

Epigenetic regulation of mammalian sex determination

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ABSTRACT

Regulation of gene expression without changing the DNA sequence is governed by epigenetic mechanisms. Epigenetic regulation is important for changing chromatin structure in response to environmental cues as well as maintaining chromatin structure after cell division. The epigenetic machinery can reversibly change chromatin function, allowing a wide variety of biological processes in multicellular organisms to be controlled. Epigenetic regulation ensures spatial and temporal accuracy of the expression of developmentally regulated genes. So far, few studies have focused on the relationship between epigenetic regulation and mammalian sex development, despite this being an interesting area of research. Sex development consists of three sequential stages: the undifferentiated stage, gonadal differentiation into testes or ovaries, and differentiation of internal and external genitalia. Some genetic studies have revealed that epigenetic regulation is required for proper gonadal differentiation in mice. Particularly, the epigenetic machinery plays an integral part in sex determination, which is the first step of gonadal differentiation. Mammalian sex determination is triggered by activation of the mammalian sex-determining gene, *Sry*, in a spatially and temporally accurate manner. Several studies have demonstrated that expression of *Sry* is controlled not only by specific transcription factors but also by the epigenetic machinery. Here, we focus on the epigenetic regulation of *Sry* expression.

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1. Introduction and overview of recent progress in epigenetic regulation in mammals

Epigenetics is the study of heritable changes in gene expression that cannot be explained by changes to the DNA sequence (Wolffe and Matzke, 1999). The essence of epigenetic regulation is the structural change of chromatin to activate or suppress gene

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expression in a developmental stage-specific manner. Epigenetic regulation mechanisms therefore play indispensable roles in mammalian development. An important characteristic of epigenetic gene regulation, unlike genetic mutations, is its reversibility. Covalent modifications of histone tails and DNA methylation (5-methylcytosine) are the major players of epigenetic regulation in mammals.

Histone modification is dynamically regulated by the opposing activities of modifying- and de-modifying enzymes. The most recently discovered histone-modifying enzymes include histone lysine methyltransferase (Rea et al., 2000) and demethylases (Shi et al., 2004; Tsukada et al., 2006). Some previous studies concluded that histone methylation is irreversible (Byvoet, 1972; Duerre and Lee, 1974). At present, it is thought that mammalian genomes contain more than 10 genes for histone lysine methyltransferases and about 20 genes for histone lysine demethylases, indicating that histone methylation levels are regulated dynamically, like phosphorylation and acetylation of histones (Bannister and Kouzarides, 2005; Hojfeldt et al., 2013; Klose and Zhang, 2007).

Enzymes that catalyze DNA methylation have been well characterized. Maintenance DNA methyltransferase 1 (Dnmt1) prefers DNA substrates that are methylated at CpG sites on one strand only, known as hemimethylated DNA (Bestor and Ingram, 1983; Li et al., 1992). Dnmt3a and Dmnt3b are the de novo DNA methyltransferases that show no preference for methylation of hemimethylated DNA (Okano et al., 1998, 1999). In contrast to DNA methylation, mechanisms of DNA demethylation have long remained controversial. Passive DNA demethylation occurs automatically for newly synthesized DNA during replication if the maintenance DNA methylation pathway is inactive. Many candidate enzymes from the known DNA-modifying pathways have been historically proposed to function in DNA demethylation; however, these candidate pathways need to be further explored (Nabel et al., 2012). It was recently found that oxidation of 5-methylcytosine by the ten-eleven translocation (TET) family of enzymes plays an important role in the active DNA demethylation processes (Ito et al., 2010; Kriaucionis and Heintz, 2009; Tahiliani et al., 2009). In this context, TET enzyme-produced 5-hydroxymethylcytosine is passively depleted through DNA replication or reverted to cytosine through further oxidation followed by the base excision repair pathway, offering a new model for a complete cycle of dynamic cytosine modification (Kohli and Zhang, 2013).

2. Epigenetics in mammalian sex determination

Epigenetic regulation of mammalian sex determination and differentiation are interesting research areas. So far, several mouse genetic studies have revealed indispensable roles of epigenetic regulation in mammalian sex determination, especially in the transcriptional regulation of the mammalian sex-determining gene, *Sry*. In this review, we introduce these findings and discuss future perspectives regarding epigenetic regulation of mammalian sex differentiation.

2.1. Histone demethylation

Histone lysine methylation occurs on H3 and H4 of core histones. Unlike histone acetylation, which generally correlates with transcriptional activation, histone lysine methylation contributes to either transcriptional activation or repression, depending on the sites of methylation (Martin and Zhang, 2005). For example, methylation of histone H3 lysine 4 (H3K4) is enriched on the promoter region of actively transcribed genes. In contrast, methylation of H3K9 is a representative epigenetic mark of transcriptionally silenced heterochromatin and is conserved from fission yeast to mammals (Nakayama et al., 2001; Peters et al., 2001). The JmjC domain-containing protein, Jmjd1a (also called Tsga/Jhdm2a/Kdm3a), is an enzyme that demethylates H3K9 (Yamane et al., 2006). Analysis of Jmjd1a-deficient mice revealed that it plays important roles during spermatogenesis (Liu et al., 2010; Okada et al., 2007) and metabolic regulation (Inagaki et al., 2009; Tateishi et al., 2009). Moreover, it was shown that XY mice deficient in Jmjd1a exhibit male-to-female sex reversal (Kuroki et al., 2013).

In mammals, either ovaries or testes are formed from the bipotential genital ridges during embryogenesis, with activity of the Y-linked gene *Sry* inducing testis differentiation in males. The temporal and spatial accuracy of *Sry* expression is required for the induction of the male pathway (Hiramatsu et al., 2009; Wilhelm et al., 2009). It was shown that *Sry* expression is significantly perturbed in Jmjd1a-deficient XY gonads at embryonic day 11.5 (E11.5) at the time of maximal *Sry* expression in wild-type testes, indicating that Jmjd1a is involved in the positive regulation of *Sry*. Jmjd1a deficiency did not induce a delay in *Sry* expression but lowered the peak in its expression in the developing gonads. Rescue experiments were performed with transgenic mice in which *Sry* was ectopically expressed from a heterologous promoter (Kidokoro et al., 2005). Forced expression of *Sry* normalized testis development, indicating that perturbed *Sry* expression is solely responsible for sex reversal of XY Jmjd1a-deficient mice (Kuroki et al., 2013).

Wt1, *Gata4*, *Cbx2*, *Map3k4*, *Igf1r*, *Nr5a1*, *Gadd45*γ are known *Sry* regulators (Ono and Harley, 2013). Expression microarray analysis of gonadal somatic cells indicated that Jmjd1a deficiency did not compromise the expression of these *Sry* regulators. Furthermore, expression levels of the genes encoding transcription factors essential for gonadal development, such as *Lhx9*, *Dax-1*, *Arx*, and *Dmrt1*, were not changed in the Jmjd1a-deficient gonads. Chromatin immunoprecipitation (ChIP) using isolated gonadal somatic cells at E11.5 demonstrated that Jmjd1a was bound to the *Sry* locus in wild-type gonadal somatic cells. Furthermore, H3K9 methylation levels within the *Sry* locus were significantly elevated in XY Jmjd1a-deficent gonads at E11.5 (Kuroki et al., 2013). Taken together, it was concluded that Jmjd1a targets *Sry* directly then removes suppressive H3K9 methylation to activate transcription (Fig. 1).

Increased levels of H3K9 methylation at the *Sry* locus in Jmjd1a-deficient gonads indicate the existence of an enzyme responsible for H3K9 methylation at this locus. Recently, Kuroki et al. identified the GLP/G9a H3K9 methyltransferase complex as the enzyme counteracting Jmjd1a-mediated H3K9 demethylation at the *Sry* locus. Based on this finding, Kuroki et al. rescued the sex-reversal phenotype of Jmjd1a-deficient mice by modulating GLP/G9a complex activity via a heterozygous *GLP* mutation that restores *Sry* expression (Kuroki et al., 2017). In addition, the administration of UNC0642, a chemical inhibitor of the GLP/G9a enzyme, into Jmjd1a-deficient embryos also successfully rescued sex reversal. This study revealed that the H3K9 methylation level at the *Sry* locus is finely tuned by the balance of activities between the H3K9 demethylase Jmjd1a and the H3K9 methyltransferase GLP/G9a complex to ensure correct *Sry* expression.

Because Jmjd1a catalyzes the demethylation of H3K9me2 and the GLP/G9a complex catalyzes H3K9 dimethylation, the H3K9me2 mark seems to be critical for the regulation of *Sry* expression. A previous study has demonstrated that not only H3K9me2 but also a significant amount of H3K9me3 is detected at the *Sry* locus (Kuroki et al., 2013). Eset is known as an enzyme responsible for H3K9 trimethylation (Yang et al., 2002). Quantitative RT-PCR analysis has demonstrated that Eset is expressed in E11.5 XY gonadal somatic cells (Kuroki et al., 2013). Kuroki et al. genetically examined the possible involvement of Eset-mediated H3K9 trimethylation in *Sry*

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