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Review

Epigenetic gene regulation by plant Jumonji group of histone demethylase ☆

Xiangsong Chen [a], Yongfeng Hu [b], Dao-Xiu Zhou [b,*]

[a] National Key Laboratory for Crop genetic Improvement, Huazhong Agricultural University, 430070 Wuhan, China
[b] Institut de Biologie des Plantes, UMR8618, Université Paris sud 11, CNRS, 91405 Orsay, France

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ABSTRACT

Histone methylation plays an important role in epigenetic regulation of gene expression. Reversible methylation/demethylation of several histone lysine residues is mediated by distinct histone methyltransferases and histone demethylases. Jumonji proteins have been characterized to be involved in histone demethylation. Plant Jumonji homologues are found to have important functions in epigenetic processes, gene expression and plant development and to play an essential role in interplay between histone modifications and DNA methylation. This article is part of a Special Issue entitled: Epigenetic Control of cellular and developmental processes in plants.

1. Introduction

In eukaryotes, genomic DNA is packaged with histones to form nucleosomes that are the basic structure of chromatin. DNA methylation and histone modifications including methylation, acetylation, phosphorylation, ubiquitination and sumoylation, etc. play critical roles in regulating chromatin structure and gene expression, mainly by altering nucleosome stability and positioning which affect accessibility for regulatory proteins or protein complexes [1]. For example, histone acetylation is usually detected in actively transcribed regions, as the negative charge of the acetyl group neutralizes the positive charge of histones to make the chromatin accessible for the transcription machinery [2]. Histone H3 lysine 9 methylation (H3K9me) provides anchor for Heterochromatin Protein 1 (HP1) that is essential for heterochromatin formation in animal cells [3].

Histone methylation mainly occurs on lysine and arginine residues of histone N-terminal tails. Histone lysines can be mono-, di-, and trimethylated [1], histone arginines can be mono- and di-methylated, where the two methyl groups can be added to one (asymmetrical) or the two (symmetrical) amine groups of arginine [4]. Each distinct methyl state may have different biological functions. For instance, dimethylation of H3K9 (H3K9me2) and trimethylation of H3K27 (H3K27me3) negatively correlate with gene activity, whereas di- and trimethylation of H3K4 (H3K4me3) and H3K36 (H3K36me3) are associated with gene expression [5]. In plants, histone methylation is an important epigenetic modification for processes including genome stability, chromatin structure, epigenetic memory as well as for developmental reprogramming such as cell fate determination [6,7] and developmental transition [8]. Plant histone methyltransferases specific to H3K4, H3K9, H3K27 and H3K36 are being characterized. Plant histone methyltransferases have been reviewed recently [7]. Here we discuss recent progress on the reversing mechanism of histone methylation in plants.

2. Histone demethylases

Histone methylation was considered as irreversible, until the discovery of Lysine Specific Demethylase 1 (LSD1) that removes mono- and dimethyl groups from H3K4 [9]. LSD1 is an amine oxidase, which needs flavine adenine dinucleotide (FAD) for its demethylase activity. Subsequently it was shown that in the presence of the androgen receptor, LSD1 can demethylate H3K9me [10]. Homologues of LSD1 are found in plants. In *Arabidopsis thaliana* and rice (*Oryza sativa*), there are 4 LSD1- like genes, respectively [11,12]. One of them in *Arabidopsis*, *FLOWERING LOCUS D* (*FLD*) has been shown to promote transition from vegetative to reproductive phase by repressing the flowering repressor *FLOWERING LOCUS C* (*FLC*) [13]. *FLD* acts partially redundantly with two other homologues, *LSD1-LIKE 1* (*LDL1*) and *LSD1-LIKE 2* (*LDL2*) [11]. In *ldl1 fld* double mutants, H3K4m2 on *FLC* locus is enriched suggesting an H3K4 demethylases activity of the two proteins [11].

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* Corresponding author.
E-mail address: dao-xiu.zhou@u-psud.fr (D.-X. Zhou).

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Table 1
Jumonji genes in Arabidopsis and rice.

Animal Jumonji protein group	Histone substrate	*Arabidopsis thaliana*	*Oryza sativa*	Function of plant proteins
KDM6/JMJD3	H3K27	–	–	–
KDM5/JARID	H3K4	JMJ14 (At4g20400)		Flowering time and DNA methylation
		JMJ15 (At2g34880, MEE27)		Female gametophyte development
		JMJ16 (At1g08620)	JMJ703 (Os05g10770)	
		JMJ17 (At1g63490)	JMJ704 (Os05g23670)	
		JMJ18 (At1g30810)	JMJ708 (Os06g51490)	
		JMJ19 (At2g38950)		
KDM4/JMJD2	H3K9/H3K36	JMJ11 (At5g04240, ELF6)		Flowering time and BR signaling
		JMJ12 (At3g48430, REF6)		Flowering time and BR signaling
			JMJ706 (Os10g42690)	Floral organ development
		JMJ13 (At5g46910)	JMJ707 (Os02g46930)	
			JMJ701 (Os03g05680)	
			JMJ702 (Os12g18150)	
			JMJ705 (Os01g67970)	
KDM3/JMJD1	H3K9	JMJ25 (At3g07610, IBM1)		Negative regulation of DNA methylation at transcribed loci
		JMJ24 (At1g09060)	JMJ715 (Os03g31594)	
		JMJ26 (At1g11950)	JMJ716 (Os03g22540)	
		JMJ27 (At4g00990)	JMJ718 (Os09g22540)	
		JMJ28 (At4g21430)	JMJ719 (Os02g01940)	
		JMJ29 (At1g62310)	JMJ720 (Os02g58210)	
KDM2/JHDM1	H3K36	–	–	–
JmjC domain only		JMJ20 (At5g63080)	JMJ709 (Os01g36630)	
		JMJ21 (At1g78280)	JMJ711 (Os03g27250)	
		JMJ22 (At5g06550)	JMJ710 (Os11g36450)	
		JMJ30 (At3g20810, JMJD5)		Circadian regulation
		JMJ31 (At5g19840)	JMJ717 (Os08g39810)	
		JMJ32 (At3g45880)	JMJ713 (Os01g56640)	
			JMJ714 (Os09g31050)	
			JMJ712 (Os09g31380)	

Plant Jumonji genes are grouped according to the conservation of their JmjC domain with animal Jumonji groups for which histone substrates are known. No plant proteins in KDM6 and KDM2 are found.

Subsequent to the discovery of LSD1, Jumonji proteins were proposed as potential histone demethylases [14]. The Jumonji protein was first identified in mouse by gene trap approach [15]. The gene was named after the morphology of the neural plates of mutant mice, which resembles a cruciform or "jumonji" in Japanese [15]. Structural analysis indicates that Jumonji proteins contain a conserved domain, called JmjC domain, which contains the conserved 2-oxoglutarate-Fe (II)-binding site found in the dioxygenase super family. Subsequently, JmjC-domain containing proteins were found to be able to remove histone methyl groups [16,17]. The demethylase activity is dependent on the JmjC domain. Substitution of the histidine residue which is critical for Fe(II) interaction disrupts the demethylase activity. Multiple JmjC domain-containing histone demethylases have been identified in animal cells, which are divided into distinct groups according to sequence similarities, including JARID/KDM5, JMJD1/JHDM2/KDM3, JMJD2/KDM4, JMJD3/KDM6, JHDM1/FBX/KDM2 and the "JmjC domain-only" group. Different groups target specific histone lysines at different methylation states [5] (Table 1).

About 20 JmjC domain-containing protein genes are found in Arabidopsis or rice [18,19] (Table 1). Most animal JmjC proteins are conserved in plants, while JMJD3/KDM6 and JHDM1/KDM2 groups that demethylate H3K27me3/2 and H3K36me2/1, respectively, are not found in Arabidopsis or rice. In addition, plant JmjC proteins contain many additional protein modules [18,19]. During the last years, functional analysis of plant JmjC histone demethylases have revealed interesting clues of epigenetic regulatory processes of chromatin function and plant development (Fig. 1) (Table 1).

3. JmjC protein function in plant gene expression and development

3.1. Plant H3K4 demethylases identified

Genome-wide analysis has indicated that H3K4me is found on about two-thirds of Arabidopsis genes [20]. Analysis of H3K4 methylation of two entire chromosomes in rice reveals that half of protein-coding genes have di- and/or trimethylated H3K4 on the chromatin [21]. H3K4me2 and H3K4me3 accumulate predominantly in 5′ genic regions in the plants [21]. Histone H3K4me3 at the 5′ region of genes is strongly associated with transcriptional activation. Rice genes with predominant H3K4me3 are actively transcribed, whereas those with predominant H3K4me2 are transcribed at moderate levels. Histone H3K4 methylation is mediated by Trithorax group proteins (TRX) and its homologues that activate homeotic gene expression in animals. Arabidopsis homologues of TRX (ARABIDOPSIS TRITHORAX 1, 2, ATX1, 2) have been shown to methylate H3K4 [22]. Other SET (named after 3 *Drosophila* genes: Su(var)3-9, enhancer of zeste and Trithorax)-domain genes such as SDG4 and SDG2 also methylate H3K4 [23–25]. Recent studies have discovered a couple of Arabidopsis JmjC genes encoding H3K4 demethylases. Mutations in Arabidopsis *JMJ14* (also called *AtJmj4*, *PKDM7B*, At4g20400) produce *Flowering Locus T* (FT)-dependent early-flowering. The mutation of the gene leads to increased expression of FT and increased H3K4me3 levels within FT chromatin [26–28]. Tagged JMJ14 protein associates directly with the FT transcription initiation region where H3K4me3 is increased most significantly in the mutants [26]. JMJ14 belongs to the JARID1/KDM5 group, members of which have been shown to display H3K4 demethylase activities (Table 1). *In vitro* and *in vivo* assays have revealed that JMJ14 also possesses specific demethylase activities for mono-, di-, and trimethylated H3K4 [26,28], indicating conservation of enzymatic function within this group of genes in plants. Another Arabidopsis member of this group, JMJ15 (At2g34880), has been shown to also demethylate all three states of H3K4 methylation *in vivo* [7]. This gene has been previously identified as *MEE27* (*Maternal Effect Embryo arrest 27*) in a screen for mutants defective in the female gametophyte development [29], suggesting a potential role of the gene in reproductive development. H3K4me3 has been found to be increased on many genes induced by signals including light and submergence, but decreased after removal of the signals [30,31]. This suggests that H3K4 methylation/demethylation may be a dynamic process. It remains to be determined whether JMJ14 and JMJ15 or other members of this group are involved in the regulation of inducible gene expression.