What Triggers Differential DNA Methylation of Genes and TEs: Contribution of Body Methylation?

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Transposable elements (TEs) are epigenetically silenced with extensive DNA methylation. The silent epigenetic marks should, however, be excluded from active genes. By genetic approaches, we study mechanisms to remove the heterochromatin marks from transcribed genes. Based on our observations on control of TE transcription, we propose a possible trigger for the TE-specific accumulation of DNA methylation. A critical difference between TEs and genes could be their responses to the DNA methylation in the internal part of transcribed regions. When their internal region is methylated, genes are still transcribed, but TEs could be silenced, which may reflect the obligatory position of every critical *cis*-acting element within the TE itself. This initial difference of TEs and genes will be amplified by positive feedback loops to stabilize active or silent states. Thus, the mechanisms to accumulate heterochromatin marks within transcribed regions could provide a trigger to induce differential DNA methylation between genes and TEs.

In plant genomes, DNA methylation of transposable elements (TEs) is important for genome stabilization and appropriate expression of cellular genes near TEs (Kakutani et al. 2004; Lippman et al. 2004; Chan et al. 2005; Huettel et al. 2006; Saze and Kakutani 2007; Mirouze et al. 2009; Tsukahara et al. 2009). Genome-wide analyses of DNA methylation have revealed that TEs are heavily methylated in cytosines in all three sequence contexts: CG, CHG, and CHH (*H* can be A, T, or C). On the other hand, the methylation level is much lower in genes and the genic methylation is limited to CG sites (Zhang et al. 2006; Zilberman et al. 2007; Cokus et al. 2008; Lister et al. 2008). A central question is what triggers the differential DNA methylation between genes and TEs.

Whereas methylation in CG sites is maintained by the maintenance CG methyltransferase MET1, TE-specific non-CG methylation is connected to other epigenetic marks for silent chromatin. Methylation at CHG sites depends on methylation of lysine 9 in histone H3 (H3K9me) (Jackson et al. 2002; Malagnac et al. 2002). H3K9me is an epigenetic mark of silent chromatin found in diverse organisms, including animals and fungi. TEs can also be methylated at asymmetric CHH sites and that is generally associated with small RNA. Small RNA is also a hallmark of silent chromatin conserved in diverse organisms (Grewal and Elgin 2007). In plants, the mechanisms controlling heterochromatin by small RNA have been extensively studied by genetic characterization of RNA-directed DNA methylation (RdDM). RdDM is an intriguing phenomenon first observed in tobacco, in which double-stranded RNA induces de novo DNA methylation of identical sequences (Wassenegger et al. 1994; Mette et al. 2000). RdDM can induce de novo DNA methylation in all three sequence contexts. Genetic screening of *Arabidopsis*

has led to identification of factors involved in RdDM, which includes the de novo DNA methyltransferase DRM2, the chromatin remodeling factor DRD1, as well as additional components of RNA interference (RNAi) and RNA polymerase complexes (Matzke et al. 2009; Law and Jacobsen 2010; Haag and Pikaard 2011).

One important feature of silent chromatin is that interactions among the various epigenetic marks generate positive feedback loops. CHG sites are methylated by the DNA methyltransferase CMT3 (chromomethylase 3). CMT3 activity depends on H3K9me at the target locus. H3K9me is catalyzed by the histone methyltransferase KYP/SUVH4 and its activity depends on methylation at CHG sites (CHGme) (Johnson et al. 2007; Inagaki et al. 2010). The interdependence of H3K9me and CHGme creates a positive feedback loop. Likewise, a positive feedback loop may operate between DNA methylation and small RNA. DNA methylation, especially at CHH sites, depends on the RdDM machinery. The generation of small RNA, on the other hand, depends on the DNA methyltransferase DRM2 (Zilberman et al. 2004; Henderson et al. 2010). These positive feedback loops would explain how chromatin silencing is enhanced, spread, and stabilized, but it does not clarify the difference that initially triggers the differential methylation of TEs and genes.

RdDM would be an important mechanism to specifically target heterochromatin to TEs. Rearrangements and nested insertions of TEs often generate tandem direct repeats and inverted repeats. In addition, a TE generally has inverted or direct repeats in the terminal regions. These repeats could be templates for small RNA and would result in DNA methylation by the RdDM process (Martienssen 2003). In mutants of RdDM machinery, however, only a few TEs are derepressed transcriptionally

(Lippman and Martienssen 2004; Xie et al. 2004; Huettel et al. 2006). That is in contrast to the effects of *met1* mutants or mutants defective in the chromatin remodeler *DDM1* that show derepression of many more TEs (Lippman et al. 2004). RdDM mutants generally affect short TEs and their derivatives, such as short interspersed elements (SINEs) (Lippman and Martienssen 2004; Herr et al. 2005) and solo long terminal repeats (LTRs) (Huettel et al. 2006). Genome-wide DNA methylation analyses, as well as small RNA surveys, also identify short TEs as targets of RdDM (Tran et al. 2005; Lee et al. 2012). The RdDM component NRPE1 localizes over the entire sequence of short TEs but localizes specifically in terminal regions of long TEs (Zhong et al. 2012). These results suggest that the internal heterochromatin of long TEs, which depends on MET1 and DDM1, does not depend on RdDM. Length seems to be an important parameter for epigenetic control of TEs and their derivatives.

In the following part of this article, we discuss transcriptional response of genes and TEs in the contexts of epigenetic modifications and sequence length and propose a possible mechanism that triggers their differential DNA methylation. The critical difference between genes and TEs could be their transcriptional responses to the change in DNA methylation within the transcribed region. The model that we propose might also be related to another question: What is the role of gene-body methylation?

INTERNAL REGIONS OF LONG TRANSCRIBED SEQUENCES ACCUMULATE CG METHYLATION

Unlike DNA methylation in TEs and repeats, genic DNA methylation is limited to CG sites (Cokus et al. 2008; Lister et al. 2008). This gene-body CG methylation is high in the central part of genes, and 5' and 3' terminal regions are not typically methylated. Interestingly, long genes have more body methylation than short genes (Inagaki et al. 2010; Takuno and Gaut 2012).

Counterintuitively, gene-body methylation is higher in transcribed genes than in untranscribed genes. The basis for this association is not clear. Loss of CG methylation in *met1* mutation does not substantially affect the expression of body-methylated genes (Zhang et al. 2006). Thus, the correlation is not attributable to an effect of body methylation on transcription. Rather, gene-body methylation could be the consequence of transcription (see further discussion below).

The mechanism for targeting body methylation is not clear. In addition, the role of gene-body methylation is not clear either. Interestingly, gene-body methylation excludes H2A.Z (Zilberman et al. 2008). H2A.Z is a histone variant conserved among eukaryotes and controls transcription in diverse manners. Although H2A.Z distribution is affected by a *met1* mutation, disruption of H2A.Z genes does not substantially affect gene-body methylation (Zilberman et al. 2008; Coleman-Derr and Zilberman 2012). Therefore, H2A.Z is not the upstream factor

determining the distribution of gene-body methylation. Rather, gene-body methylation, which may be controlled by transcription, seems to be the upstream factor.

INTERNAL REGIONS OF LONG TRANSCRIBED SEQUENCES ACCUMULATE CHG_{ME} AND H3K9_{ME} WHEN THE IBM1 HISTONE DEMETHYLASE IS NONFUNCTIONAL

The body of long genes also has the potential to accumulate TE-specific epigenetic marks, such as H3K9_{me} and CHG_{me}. By a genetic screen of *Arabidopsis* mutants showing ectopic cytosine methylation in a genic region, we identified a novel H3K9 demethylase gene *IBM1* (*increase in bonsai methylation1*). The *ibm1* mutation induces ectopic H3K9_{me} and CHG_{me} in thousands of genes (Saze et al. 2008; Miura et al. 2009; Inagaki et al. 2010). Both H3K9_{me} and CHG_{me} are TE-specific epigenetic marks in the wild type, but they are found in genes in the *ibm1* mutant. The *ibm1* mutation affects constitutively expressed genes and long genes. Central regions of transcription units are affected, whereas 5' and 3' terminal regions are not affected. This spectrum of *ibm1*-affected genes is strikingly similar to that of gene-body methylation at CG sites in wild-type plants (Miura et al. 2009; Inagaki et al. 2010). This similarity suggests that gene-body CG methylation may have a causative relationship with CHG_{me} that is revealed when the function of H3K9 demethylase IBM1 is masked (Saze and Kakutani 2011). Again, transcription could be a common upstream factor to induce the accumulation of these marks within the transcription unit.

TRANSCRIPTION OF GENES IS AFFECTED BY DNA METHYLATION IN PROMOTERS BUT NOT IN INTERNAL REGIONS

Notably, increased CHG_{me} and H3K9_{me} in the *ibm1* mutant does not substantially affect the expression of the target genes. Similarly, the loss of CG methylation in *met1* does not affect the expression of most body-methylated genes (Zhang et al. 2006). These results indicate that DNA methylation and H3K9_{me} in internal regions generally do not affect the transcription of genes.

Although DNA methylation in internal regions has a limited effect on expression, DNA methylation at promoters or 5' terminal regions is associated with gene silencing. DNA methylation is found in the promoters of *SDC* and *FWA* genes and these genes are derepressed in mutants of DNA methyltransferases (Soppe et al. 2000; Kinoshita et al. 2004; Lippman et al. 2004; Henderson and Jacobsen 2008). Interestingly, promoters of these genes have features similar to short TEs and repeats (Lippman et al. 2004; Fujimoto et al. 2008; Henderson and Jacobsen 2008). In addition, changes of DNA methylation in TEs often affect expression of nearby genes (Huettel et al. 2006; Saze and Kakutani 2007). In summary, transcription of genes can be affected by DNA

methylation in the promoter or even surrounding outside regions, but DNA methylation in internal regions does not affect the transcription of genes substantially.

UNLIKE GENES, TRANSCRIPTION OF TEs CAN BE AFFECTED BY DNA METHYLATION IN BOTH PROMOTER AND INTERNAL REGIONS

In an *Arabidopsis met1* mutant, a large number of TEs are up-regulated. These activated TEs include both promoter-methylated and body-methylated types, suggesting possible roles for both domains of methylation in TE silencing (Zhang et al. 2006).

Derepression of TEs is also found in *cmt3* and *kyp* mutants. Importantly, this TE transcription decreases when these mutations are combined with an *ibm1* mutation (Inagaki et al. 2010). In the double mutants *ibm1-kyp* or *ibm1-cmt3*, H3K9me levels are increased in the central regions of TEs, which is associated with transcriptional silencing. This is in striking contrast to the *ibm1*-induced increase of H3K9me in gene bodies; although increased H3K9me and CHGme in the transcribed region does not affect the transcription of genes, the internal heterochromatin marks affect transcription of these TEs.

Taken together, these observations are consistent with the idea that the silencing of TEs can be regulated by DNA methylation not only in the promoter but also in the internal region. What could be the basis for the difference between transcriptional responses of TEs and genes? An intact TE brings its *cis*-acting elements during transposition. Therefore, *cis*-acting elements critical for transcription, such as a methylation-sensitive enhancer, should be within a TE itself, often localizing in the transcribed regions (Fig. 1, bottom). The situation is different in genes, which can be controlled by enhancers that are further away from transcribed regions (Fig. 1, top). Genes evolve to coordinate transcription using surrounding *cis*-acting elements. In contrast, TEs have evolved to control their expression independently, so that the control

works even after transposition to a different genomic environment.

HYPOTHESIS

Assumption 1. Transcription induces accumulation of H3K9me and CHGme in the internal region of transcription unit for both TEs and genes.

Assumption 2. H3K9me and CHGme in the internal region inhibit transcription of TEs, but not genes.

Model. Transcription induces accumulation of H3K9me and DNA methylation in the internal region for both genes and TEs (Fig. 2, top). These modifications result in silencing of TEs but not genes (Fig. 2, middle). Genes remain transcribed, which induces active H3K9 demethylation by IBM1 (Fig. 2, bottom right). On the other hand, IBM1-induced H3K9 demethylation is not efficient in the silenced TEs. In silenced TEs, the H3K9me and CHGme enhance each other and spread to terminal regions including the promoter, making the TE silencing more robust and stable (Fig. 2, bottom left).

HOW GENERAL?

A key feature in the model that we propose is that body methylation could affect the transcription of TEs, because they should have promoter/enhancer elements within the TE itself. This seems a general feature of TEs, but the situation might differ among TEs because their structures as well as controls are diverse.

TEs often have mechanisms to counteract silencing by the host. *Spm* elements in maize spontaneously switch activity between silent and active states, which correlates with changes in DNA methylation status in the UCR (upstream controlling region) and DCR (downstream controlling region). Loss of methylation can be induced by TnpA, a protein encoded by *Spm* (Schläppli et al. 1994; Cui and Fedoroff 2002). TnpA is able to induce loss of methylation in both the UCR and DCR. Interestingly, deletion of the DCR stabilizes the expression of reporter

Figure 1. Transcription of a gene can be controlled by *cis*-acting elements surrounding it, but TEs should keep these *cis*-acting elements within itself. The gene (*top*) will evolve to coordinate transcription using surrounding *cis*-acting elements, some of which are methylation sensitive and even evolved from TEs. The TE (*bottom*) should evolve to control its transcription using *cis* elements within itself, because the control should work after transposition to different genomic environments.

Figure 2. Differentiation of genes and TEs, by differential response to body methylation. For both genes and TEs, transcription of the long transcription unit induces accumulation of DNA methylation and H3K9me (green arrow; *top panel*). Heterochromatin in the body suppresses transcription of the TE (red bar; *middle left*), but genes are not affected (*middle right*). In genes, transcription induces loss of H3K9me and CHGme by action of the IBM1 demethylase (blue bar; *bottom right*). CGme in the gene body does not spread but is maintained by maintenance methylation. In the TE, without function of IBM1, H3K9me and CHGme spread by a positive feedback loop (orange double arrow; *bottom left*), making the silencing more robust with promoter methylation.

transgenes (Schläppli et al. 1994). The DCR, which is localized within the transcribed region, mediates the silencing, most likely by controlling epigenetic states.

Mutator is another transposon characterized well in maize. Reversible change in *Mutator* activity correlates with DNA methylation in terminal regions as well as internal regions (Chandler and Walbot 1986; Brown and Sundaresan 1992). Silent *Mutator* can be activated sporadically by the *mop1* mutation. The *MOP1* gene encodes a protein similar to *Arabidopsis* RDR2 (RNA-dependent RNA polymerase 2), which is involved in RdDM (Lisch et al. 2002; Alleman et al. 2006). In *Arabidopsis*, mutations in RdDM components generally affect terminal regions of long TEs. Methylation in terminal regions may be important for maize *Mutator* elements. Interestingly, however, although the *mop1* mutation causes loss of methylation in the terminal regions immediately, expression of *mudrA* occurs progressively, possibly reflecting additional epigenetic factor(s) in addition to the DNA methylation in the terminal regions (Lisch et al. 2002). It would be interesting to learn if heterochromatin in the internal region is involved.

PERSPECTIVE

We propose that TEs could be specifically silenced by the mechanism to accumulate epigenetic marks within transcribed regions (Fig. 2, top). Dependence of heterochromatin formation on transcription has been suggested in a fission yeast *Schizosaccharomyces pombe*. In *S. pombe*, a mutant allele of Pol II causes a defect in silencing (Kato et al. 2005). In plants, a transcript of Pol V that is related to Pol II is suggested to form a scaffold for silencing machinery (Wierzbicki et al. 2008, 2009).

Another key feature in the model is the positive feedback loop between CHGme and H3K9me that causes spreading of heterochromatin from the body to the promoter. The H3K9 methyltransferase KYP/SUVH4 has an SRA domain that recognizes CHGme (Johnson et al. 2007). Mutations in the *KYP/SUVH4* gene suppress the *ibm1*-induced increase in H3K9me almost completely (Inagaki et al. 2010). However, in the *kyp/suvh4* mutant, H3K9me reduction of endogenous TEs is not complete (Inagaki et al. 2010), suggesting that other H3K9 methyltransferases may be involved. Some H3K9 methyltransferases are suggested to be regulated by DNA methylation in contexts other than CHG (Johnson et al. 2008). These interactions might mediate the simultaneous accumulation of CG and non-CG methylation in the body of transcribed sequences (Fig. 2, top). Although IBM1 excludes H3K9me and DNA methylation at non-CG sites, methylation in CG sites is retained by maintenance methylation catalyzed by MET1 (Fig. 2, bottom right).

The accumulation of both CGme and CHGme are mainly found in long transcription units. Such mechanisms, which would be efficient for silencing long TEs, would probably complement RNAi-based mechanisms that function mainly on short TEs. Although silencing of long TEs tends to be stable and constitutive, control of short TEs could be more dynamic. DNA demethylation in short TEs occurs during development. Genome-wide loss of DNA methylation is found in endosperm and pollen vegetative cells (Gehring et al. 2009; Hsieh et al. 2009; Slotkin et al. 2009; Schoft et al. 2011; Calarco et al. 2012; Ibarra et al. 2012). In those companion cells of germlines, loss of methylation mainly occurs in short TEs. Long TEs lose methylation only in terminal regions and internal regions remain methylated (Ibarra et al. 2012). Again, the length seems a critical parameter.

We still do not know the exact nature of interactions among various epigenetic marks, some of which are dynamic whereas others are stable. The *ibm1* mutation affects long transcription units and the effects of this mutation become stronger after repeated self-pollinations (Saze et al. 2008). H3K9 demethylation of transcribed genes (Fig. 2, bottom right) may occur in a specific developmental window. It would be interesting to learn how short-term effects of epigenetic changes can be converted to long-term effects.

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