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DNA methylation in higher plants: Past, present and future☆

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ABSTRACT

A relatively high degree of nuclear DNA (nDNA) methylation is a specific feature of plant genomes. Targets for cytosine DNA methylation in plant genomes are CG, CHG and CHH (H is A, T, C) sequences. More than 30% total m^5C in plant DNA is located in non-CG sites. DNA methylation in plants is species-, tissue-, organelle- and age-specific; it is involved in the control of all genetic functions including transcription, replication, DNA repair, gene transposition and cell differentiation. DNA methylation is engaged in gene silencing and parental imprinting, it controls expression of transgenes and foreign DNA in cell. Plants have much more complicated and sophisticated system of the multicomponent genome methylations compared to animals; DNA methylation in plant mitochondria is performed in other fashion as compared to that in nuclei. The nDNA methylation is carried out by cytosine DNA methyltransferases of, at least, three families. In contrast to animals the plants with the major maintenance methyltransferase MET1 (similar to animal Dnmt1) inactivated do survive. One and the same plant gene may be methylated at both adenine and cytosine residues; specific plant adenine DNA methyltransferase was described. Thus, two different systems of the genome modification based on methylation of cytosines and adenines seem to coexist in higher plants. This article is part of a Special Issue entitled: Epigenetic control of cellular and developmental processes in plants.
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1. Past

1.1. Minor bases in DNA of plants and other organisms

60 years ago it was established that higher plant DNA contain 5-methylcytosine (m^5C) in addition to four ordinary bases (G, A, T, C) [1]. Unfortunately, at that particular time the data on the higher plant DNA base composition were extremely scanty. In fact, they were restricted to wheat germ DNA. Later the first more or less systematic investigations of DNA base composition performed under Professor A.N. Belozersky showed that 5-methylcytosine is an obligatory base for all higher plant DNA including archegoniates and flowering plants [2]. Besides, the m^5C content in plant DNA was considered even a feature of some taxonomic significance because, as a rule, the flowering plant DNAs contained more m^5C than DNAs of archegoniates, and the m^5C content was higher in DNA of monocots compared with DNA of dicots [2]. Unlike bacterial DNA plant DNA has been found to contain large quantities of m^5C so that it could hardly be considered a minor base: very often its content is comparable to that of cytosine. Later N^6-methyladenine (m^6A) in higher plant DNA was detected [3].

For a long time, the origin of methylated bases in DNA remained unknown. The attempt to detect incorporation of radioactive m^5C or its nucleosides into DNA in the *in vivo* experiments with various plants was unsuccessful [4]. Only in 1963 the specific enzymes capable of selectively methylate certain cytosine and adenine residues in DNA strands in the presence of the methyl group donor, S-adenosyl-L-methionine (SAM or AdoMet), were described in bacteria [5] and then in eukaryotes. It became clear that m^5C and m^6A are not incorporated into DNA at the template level in the ready-made form as respective nucleotides, but appear due to enzymatic modification (methylation) of the ordinary bases (C or A, respectively) in pre-existent DNA strands. However, specificity and functional role of enzymatic DNA methylation in higher plants remained unclear. Moreover, the idea that "minor" bases did not play any important role in the DNA structure and functioning was very popular. Classical object of traditional genetics, *Drosophila melanogaster*, served as an "undeniable" argument in favor of these ideas. Indeed, for a long time, m^5C was not detected in the genome of this insect. Therefore, it was wrongly concluded by some leading scientists that this DNA modification plays no essential role in the life of eukaryotic organisms. At present, it is well documented that *Drosophila* DNA is methylated and this DNA modification is essential for normal insect development [6,7]. Anyhow, we were always sure that minor DNA bases cannot be of no significance to the genome structure and functioning.

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1.2. Sequence-specificity of cytosine DNA methylation in plants

Analyzing pyrimidine sequences (clusters) obtained from wheat DNA at a time when the DNA sequencing methods were still not elaborated, we have demonstrated that 5-methylcytosine in plant genome was located in the sequences *Pu–m^{5}C–Pu, Pu–m^{5}C–T–Pu, Pu–m^{5}C–C–Pu*, and *Pu–m^{5}C–m^{5}C–Pu* [8]. These findings were consistent with the data on methylation of cytosine residues in plant DNA obtained by a nearest-neighbor analysis method, reported at the same time by A. Razin and colleagues [9]. According to our data, substantial proportion of 5-methylcytosine (about 30%) was located in m^{5}CHG sequences of plant genome [8]. For a long period, the presence of m^{5}C in CHG sites, especially in animals, was denied, and the first reports on the matter were met with suspicion and even rejected. Nevertheless, it is quite clear now that this type of DNA methylation actually takes place, and is of high biological significance. Methylation of cytosine residues in these and asymmetric DNA sequences is mostly observed upon RNA-directed methylation of genes, associated with their silencing [10]. In plants an enzyme was described that *de novo* methylates cytosine residues in any non-CG context and specifically evades CG sites [11].

DNA methylation of plant genomes is more extensive and affects a wider sequence diversity than in animals. It involves a larger set of specific DNA methyltransferases, some of which have no analogs in animals [12,13]. Maintenance methylation of CG sites is carried out by DNA methyltransferase MET1 both during DNA replication and postreplication. A chromatin-remodeling protein DDM1 and three highly related SRA domain containing m^{5}C-binding proteins, VIM1–VIM3, are most important assistants of MET1. A plant-specific chromomethylase CMT3 is major enzyme performing methylation of CHG sites, probably also in maintenance mode. A histone H3K9 methyltransferase KYP and CMT3 seem to be mutual helpers: CMT3 binds and methylates CHG sites in the H3K9/K27 methylated chromatin loci, whereas KYP binds and methylates histone H3 molecules in cytosine methylated loci. Not surprisingly the effects of *cmt3* and *kyp* mutations are quite similar. Asymmetric CHH sites cannot be methylated in a semi-conservative manner. Their methylation status in dividing cells is maintained by RNA-directed *de novo* DNA methylation (RdDM) activity of DRM methyltransferases with some help from CMT3. The DRM methyltransferases are probably responsible for *de novo* methylation of cytosine residues in all sequence contexts leading to creation of new methylated sites of all three types. It can be thus concluded that the chemical nature of the DNA methylation specificity in plants has been established. Apparently, along with the specific action of DNA methyltransferases, the degree and specificity of DNA methylation is in many respects determined by structural organization of chromatin and by accessibility of DNA sites to be methylated. This undoubtedly means that investigation of the genome methylation requires the studies of chromatin.

Concerning biological specificity of DNA methylation in eukaryotes, it should be noted that its species- and tissue-specificity was well documented long time ago. We have established that global DNA methylation degree in plants and animals is not only species-, but also tissue- (cell), subcellular (organelle-), and age-specific. We happened to be the first to find that DNA methylation status varies in different cells of an organism [14]. This finding allowed us to suggest that DNA methylation is the mechanism regulating gene expression and cell differentiation.

1.3. Replicative DNA methylation

The cultivation of plant and animal cells in the medium under conditions of high cell concentration results in a stop of DNA synthesis at the stage of Okazaki fragments, which have been found to contain m^{5}C [15–17]. Thus, replicative DNA methylation, independently predicted in 1975 by Holliday and Pugh [18] and Riggs [19], in plants and animals has been discovered. It was suggested that DNA methyltransferases can be a part of DNA replication complex [15–17]. The Okazaki fragments differ from longer ligated intermediates of replication, as well as from mature DNA in specificity and level of methylation. Unlike the methylation of ligated DNA, methylation of the Okazaki fragments is tolerant to some methylation inhibitors (S-isobutyladenosine and others) and not repressed by auxins.

In the following studies we succeeded in discrimination of the replicative and postreplicative DNA methylations in plants [20]. We proposed that methylation could be involved in the control of DNA replication and described the corresponding mechanism. It has been demonstrated that replication of plant DNA results in the production of asymmetrically methylated DNA duplexes, the methylation level of newly formed daughter strands being significantly lower as compared to mother strands. This strand asymmetry gradually decreases up to the end of the cell cycle and totally disappears before the new round of DNA replication starts. All this was directly demonstrated by m^{5}C measurement in newly formed and pre-existent strands isolated by cesium chloride density gradient centrifugation at different stages of the cell cycle. Replication of asymmetrically methylated DNA molecules in dividing cells was suggested to be somehow prohibited since it would lead to the loss of epigenetic marks.

2. Present

2.1. DNA demethylation by excision of m^{5}C residues

Mechanisms removing methylated bases from DNA has been a matter of confusion and debate for a quite long time. Passive delution of methylated bases by DNA replication in the absence of maintenance methylation has been regarded as the only self-evident and indisputable mode of selective demethylation of DNA sequences leading to developmental activation of silent genes. Thus, it was generally believed that a genome-wide DNA demethylation soon after fertilization in mammals occurs by such passive mechanism. This view was seriously shaken in 2000 when selective demethylation of paternal DNA sequences has been found to occur in few hours after fertilization before first round of DNA replication [21,22]. Two important points follow from this finding. First, an active, probably enzymatic, mechanism of DNA demethylation does exist. Second, this mechanism can be selectively targeted to paternal DNA sequences, thus creating asymmetry in cytosine methylation between two parental genomes. The nature of DNA demethylating activity in animals still remains a matter of debate (see [23,24] for a detailed discussion). In plants the mechanisms of active DNA demethylation are reasonably well understood.

DEMETER (*DME*) was first discovered as a gene normally expressed in the central cell of the female gametophyte, where its expression is needed for activation of maternal alleles of an imprinted Polycomb gene *MEDEA* (*MEA*) [25]. *DME* encodes a large protein with DNA glycosylase and nuclear localization domains. An obvious suggestion was that it activates *MEA* by excision of some methylated cytosine residues, though the sequence of the target gene appeared to be unmethylated. It was found later that DME is indeed a m^{5}C-specific DNA-glycosylase-lyase that carries out an initial activation of maternal *MEA* allele by removing 5-methylcytosine residues from two compact regions upstream and downstream of its coding sequence [26]. Paternal allele escapes this demethylating activation since *DME* is normally expressed in the central cell only before fertilization. Interestingly, the *MEA* paternal allele silencing maintained subsequently in the endosperm is not dependent on its methylation. It is carried out by maternally expressed MEA and probably some other Polycomb group proteins. Thus, MEA controls imprinting of its own gene.

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