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Review

A chromatin perspective of plant cell cycle progression ☆

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ABSTRACT

The finely regulated series of events that span from the birth of a cell to the production of two new born cells encompass the cell cycle. Cell cycle progression occurs in a unidirectional manner and requires passing through a number of stages in response to cellular, developmental and environmental cues. In addition to these signaling cascades, transcriptional regulation plays a major role and acts coordinately with genome duplication during S-phase and chromosome segregation during mitosis. In this context, chromatin is revealing as a highly dynamic and major player in cell cycle regulation not only owing to the changes that occur as a consequence of cell cycle progression but also because some specific chromatin modifications are crucial to move across the cell cycle. These are particularly relevant for controlling transcriptional activation and repression as well as initiation of DNA replication and chromosome compaction. As a consequence the epigenetic landscape of a proliferating cell is very complex throughout the cell cycle. These aspects of chromatin dynamics together with the impact of epigenetic modifications on cell proliferation will be discussed in this article. This article is part of a Special Issue entitled: Epigenetic Control of cellular and developmental processes in plants.

1. Introduction

The cell division cycle is constituted by the series of unidirectional and highly regulated events that occur between the birth of a cell and its division into two daughter cells. It requires that all cellular components duplicate to be eventually delivered to the new cells. During the S-phase the genome is duplicated and in mitosis (M) the fully duplicated genome is segregated into the two daughter cells. These two phases are temporally separated by other two phases, originally known as "gap" phases (G1 and G2), which are mostly preparatory of the S and M phases that follow G1 and G2, respectively. Errors in the complex processes occurring during cell cycle progression have consequences in the production and integrity of the daughter cells. Given the dependence of cell proliferation on development, and *vice versa*, it is of primary importance that they are strictly coordinated [1]. Proliferating cells eventually respond to internal signals (hormones, positional cues, developmental signals) and external signals and exit the cell cycle to take various differentiation pathways.

In the case of plant cells, in addition to the oscillating activity of various CDK-cyclin complexes [2], more than a thousand genes show a cell cycle-dependent transcription profile [3]. This strongly suggested that transcriptional regulation is also of primary importance in plant cell cycle progression, a view that is being supported by recent data [4]. In fact different transcriptional waves have been now identified that define key cell cycle transitions: (i) the entry into the cell cycle of arrested cells, (ii) the G1/S transition (iii) the G2/M transition, and (iv) the switch from the cell cycle to the endocycle. These various waves of transcriptional activity during the cell cycle are the consequences of transcription factor (TF) availability and binding. Although the major interactions occur between a TF and its binding site in the DNA sequence, the genome is not naked DNA but chromatin, a highly dynamic macromolecular complex of DNA, histones and non-histone proteins.

The accessibility of TFs and the transcriptional machinery to specific chromatin sites depends largely on the presence of a suitable structure and organization of the surrounding chromatin. To this end, factors such as nucleosome positioning and histone composition, DNA methylation and post-translational modification of histones are crucial [5–9]. Available data reveal that most of these marks change along the cell cycle, raising the question as to whether some of these chromatin changes can actually drive cell cycle transitions [10], as it has been shown in animal systems [7,11–13].

The major players in the epigenetic stage, the so-called epigenetic modifiers, are chromatin remodeling complexes, histone chaperones, DNA methylases, histone modification enzymes and non-coding RNAs [14–17]. Together, they very significantly increase the genetic information contained in the DNA sequence leading to an extraordinary combination of multiple covalent modifications in DNA and, particularly, in histones. The N-terminal tails of all four nucleosomal

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core histone, but especially histone H3, and to a lesser extent histone H4, are accessible to nuclear factors and can be covalently modified by acetylation, methylation, (the two best characterized modifications), phosphorylation, ubiquitylation, among others less well-characterized [15,18]. A key aspect of the histone modification machinery is the high specificity of these enzymes. To illustrate this point, different histone acetylases use as substrates specific lysine residues in the H3 tail. Likewise, a particular lysine residue can be mono-, di- or trimethylated but different enzymes introduce the different methylation states, which may have distinct consequences on chromatin accessibility. Furthermore, transcription factor binding site recognition and assembly of the transcriptional machinery is affected by the methylation state of cytosines in DNA.

2. Commitment to cycle: G1 phase and G1/S transition

The entry into the cell cycle, that is, the recruitment of arrested cells into the proliferating pool of cells, is still poorly understood. It is known that certain transcription factors act very early at this stage to eliminate the function of cell cycle repressors and increase the activity of cell cycle activators. Thus, a DOF (DNA-binding-with-one-finger) transcription factor, named OBP1, has been identified as a regulator of the expression of CYCD3;3 and members of the CDK inhibitor family KRP, positive and negative cell cycle regulators, respectively [19]. In addition, KRPs are also negatively regulated by the NAC family transcription factor NTM1 (At4g01540) [20]. Once cells are recruited into the proliferating pool they initiate the cell cycle progressing through the G1 phase and, eventually make the G1/S transition. This depends mainly on the activation of the E2F/DP family of transcription factors, which are negatively regulated by the retinoblastoma-related (RBR) protein [4,21]. Phosphorylation of RBR by (possibly various) CDK/CYC complexes release RBR repression of E2F/DP and a cohort of genes encoding for proteins required for genome duplication, e.g. several *ORC* genes, *CDC6*, *CDT1*, among others, is expressed [22–25]. In addition, some of these factors, e.g. CDT1, together with associated histone acetyltransferases, facilitate chromatin decondensation necessary for loading of other DNA replication factors [26]. This wave of transcriptional regulation is characteristic of both animal and plant cells, including unicellular algae [21,27]. Changes at the chromatin level are associated to the activation of gene expression at this cell cycle stage, including the recruitment of DNA methylases and histone acetylases, deacetylases and methyltransferases [28–30].

Genome-wide analysis [22,25,31] as well as extensive microarray data of synchronized cells [3,32,33] have shown that genes encoding for a variety of chromatin remodeling and modification factors are potential E2F target genes. Examples of this are the large subunit of chromatin assembly factor 1 (CAF-1; [34]), which deposits histone H3–H4 dimers at the DNA replication fork, or members of the Trithorax complex, responsible for trimethylation of histone H3 at lysine 4 (H3K4me3). Interestingly, the Arabidopsis large subunit of the origin recognition complex, ORC1, which is encoded by an E2F target gene, has been shown to act as a transcriptional activator of genes enriched in H3K4me3 in their promoters, including several G1/S genes such as CDT1a, MCM3 and ORC3 [35]. This is mediated by the ability of ORC1 to bind specifically to this modified histone residue through a PHD motif present in its N-terminus. The presence of the PHD is characteristic of all plant ORC1 proteins surveyed, while it is absent from yeast and animal ORC1, pointing to an evolutionary divergence in the mechanism of transcriptional control by ORC1. Therefore, ORC1 appears as a new player in controlling the expression of a subset of cell cycle genes acting as a transcriptional activator [35], although the entire set of target genes and their relevance for transcriptional control of the cell cycle remains to be investigated in more detail.

Recruitment of E2F factors in mammalian cells to their target promoters correlates with the presence of typical activation marks in the core histone, e.g. acetylated histones H3 (H3ac) and H4 (H4ac) [36,37]. A strict balance between the activity of histone acetylases (HATs) and deacetylases (HDACs) is crucial for maintaining a correct acetylation pattern at target promoters, ultimately, contributing to a more open or close chromatin conformation (Fig. 1). Some of these enzymes are also subject to a cell cycle regulated expression as illustrated by the GCN5-related histone acetyltransferase HAG2 or the plant-specific histone deacetylases HDT1-4 [10,38]. The activity of HAM, the MYST-type histone acetyltransferases, is essential for gametogenesis in Arabidopsis [39], because its loss results in mitotic arrest, although whether the sensitive phase is G1 or a later stage is not presently known. In mammalian cells, Rb recruits HDAC, either through direct interaction [40,41] or through the Rb-associated protein RBP1 [42]. The Rb–HDAC complex is stably bound to E2F target genes in G1 and is released after Rb phosphorylation at the G1/S transition [43,44]. Given the significant conservation of these proteins, their modular organization and in many cases also their interactions to regulate cell cycle transitions in plants, it is likely that similar interactions at the chromatin level can also occur. At least, the interaction of these proteins has been demonstrated in tomato and maize [45–48].

Arabidopsis contains three types of DNA methyltransferases that covalently attach methyl groups to the C residues in DNA. METHYLTRANSFERASE 1 (MET1) is a DNA methylase of CG sites that must act coordinately to DNA replication (Fig. 1). CHROMOMETHYLASE 3 (CMT3) mainly acts as a maintenance methyltransferase. Interestingly, both MET1 and CMT3 mRNA levels increase at the G1/S transition [3], compared to arrested cells, although CMT3 mRNA levels continue to accumulate at later times during the cell cycle [10,38]. Consistent with this expression pattern, both MET1 and CMT3 contain E2F binding sites in their promoters [31]. Furthermore, MET1 expression is upregulated in plants that overexpress E2F [49]. Therefore, it seems clear that MET1 is an E2F target. This is reinforced by the recent observation that RBR, in cooperation with the RBR-interacting protein MULTICOPY SUPPRESSOR OF IRA 1 (MSI1), a homologue of the RbAp48 human protein), represses MET1 expression in the central cell of the female gametophyte [50], which is required for maintenance of heterochromatin state [51]. This finding has also pointed to the involvement of RBR in the control of imprinting, a topic that is reviewed elsewhere in this issue. The third DNA methylase, DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2) is a de novo DNA methyltransferase, targets CHH sequences and does not show any apparent cell cycle regulation. Their role in DNA methylation and maintenance has been recently reviewed [9].

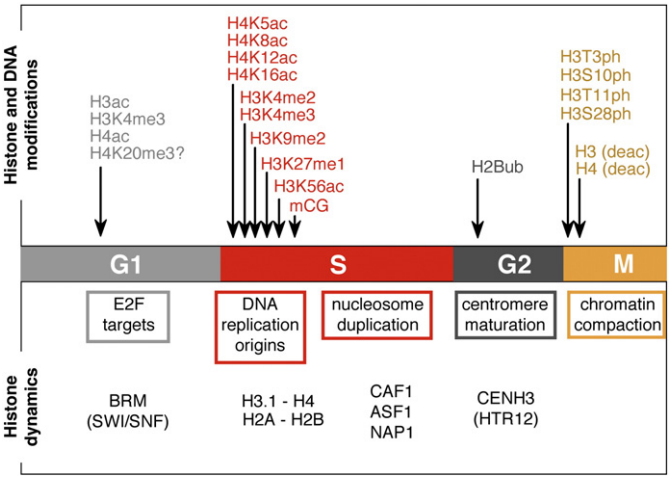

Fig. 1. Cell cycle and chromatin modifications. Schematic view of the cell cycle phases and the more representative histone modifications associated (upper part). In the lower part of the figure the main nucleosome remodeling complexes (G1), histone chaperones (S-phase) required for cell cycle progression and histones involved are indicated.