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Review

Histone lysine methylation and chromatin replication ☆

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ABSTRACT

In eukaryotic organisms, the replication of the DNA sequence and its organization into chromatin are critical to maintain genome integrity. Chromatin components, such as histone variants and histone post-translational modifications, along with the higher-order chromatin structure, impact several DNA metabolic processes, including replication, transcription, and repair. In this review we focus on lysine methylation and the relationships between this histone mark and chromatin replication. We first describe studies implicating lysine methylation in regulating early steps in the replication process. We then discuss chromatin reassembly following replication fork passage, where the incorporation of a combination of newly synthesized histones and parental histones can impact the inheritance of lysine methylation marks on the daughter strands. Finally, we elaborate on how the inheritance of lysine methylation can impact maintenance of the chromatin landscape, using heterochromatin as a model chromatin domain, and we discuss the potential mechanisms involved in this process. This article is part of a Special Issue entitled: Methylation Multifaceted Modification — looking at transcription and beyond, edited by Dr. Johnathan Whetstine.

1. Introduction

In eukaryotes, the genetic material is organized in a nucleoprotein-complex called chromatin. Within its building block, the nucleosome, 147 base pairs of DNA are wrapped around an octamer of histone proteins, including two copies each of the core histones H3, H4, H2A, and H2B [1]. This basic unit is versatile showing distinct variations including DNA methylation, histone variants, and post-translational modifications of histones (reviewed in [2,3]). In turn, these marks can either alter the structure directly or through recruitment of chromatin-binding proteins that impact the chromatin state and various processes acting on DNA including replication, transcription, and repair. Notably, to access to the DNA sequence during these processes chromatin organization is transiently disrupted. These dynamics can challenge the maintenance of information conveyed at a chromatin level and in turn could impact gene expression profiles, cell identity and function. Thus, in all of these instances a proper chromatin reassembly is a critical step to consider. DNA replication with a doubling of the genomic material poses a particular challenge since it is accompanied by a genome-wide effect on chromatin that undergoes destabilization and re-assembly on the two daughter strands. Therefore, replication has been envisioned as a window of opportunity to change the chromatin landscape and thus of importance to evaluate maintenance versus switch in gene expression profiles. In addition, an unfaithful duplication of the DNA sequence and its organization into chromatin could also affect genome function. Thus, coordinating the faithful duplication of the DNA sequence and its organization into chromatin is important to consider to maintain/alter genome and epigenome integrity.

Histone modifications have been implicated in regulating cellular activities at defined genomic loci (reviewed in [3,4]). In this review, we focus specifically on methylation of lysine residues. An extensively-documented correlation between methylation and a DNA metabolic process is transcription, where the enrichment in H3K9me3, H3K27me3, and H4K20me3 associates with transcriptionally inactive regions, contrasting with H3K4me3 and H3K36me3 that mark transcriptionally active regions [3,4]. The recent emergence of a connection between histone lysine methylation and DNA replication lead us to review these pioneering studies in order to address how methylation at specific residues and to different extents (either mono-, di-, or trimethylation) impact early steps in DNA replication. In turn, we discuss how DNA replication impacts the propagation of these methylation marks to the daughter strands, an important parameter in epigenetic inheritance during

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cellular divisions. Finally, beyond the nucleosomal level, we review possible mechanisms that participate to restore the histone lysine methylation state on defined chromatin domains. For this we use pericentric heterochromatin as a model, a well-characterized chromatin domain enriched in H3K9me3 and H4K20me3, marks that are critical for proper centromere function and chromosome segregation.

2. Histone lysine methylation: a role in early replication steps?

We distinguish here four typical phases (Fig. 1) during replication in which we can highlight proposed roles for histone lysine methylation. First, recognition of replication origins by the origin recognition complex (ORC); second, recruitment during early G1 phase of the cell division control protein 6 (CDC6) and the minichromosome maintenance (MCM) complex to ORC binding sites, forming the pre-replication complex (preRC) in a process referred to as "licensing"; third, "firing" of the origins at the entry to S-phase, mediated by the action of kinases including the cell division control protein 45 (CDC45) (reviewed in [5–7]); fourth, "elongation" (reviewed in [6]). In this section we restrict our discussion to lysine methylation and how this mark on histones H3 and H4 may impact different aspects of DNA replication (Table 1).

2.1. Origin recognition

How origins are identified in metazoans remains largely unknown, and to date no consensus sequence has been described to sufficiently predict origin identification [8]. Thus, dynamic features determined by either DNA structural elements such as G-quadruplexes [9] or chromatin-related factors have attracted attention as they may provide a signal for early steps in DNA replication (for review see [10,11]). Here we highlight possible links between histone methylation and chromatin replication (Fig. 1). In a first example, peptide arrays of 82 histone peptides featuring different methylation marks enabled the identification of ORC components that bind to distinctly methylated peptides [12]. Human ORC1, a protein that features a bromo-adjacent homology (BAH) domain (reviewed in [13]), specifically binds a peptide presenting H4K20me2 [14]. Sub-cellular fractionation further supported this binding since abrogation of the BAH recognition domain impaired ORC1 binding

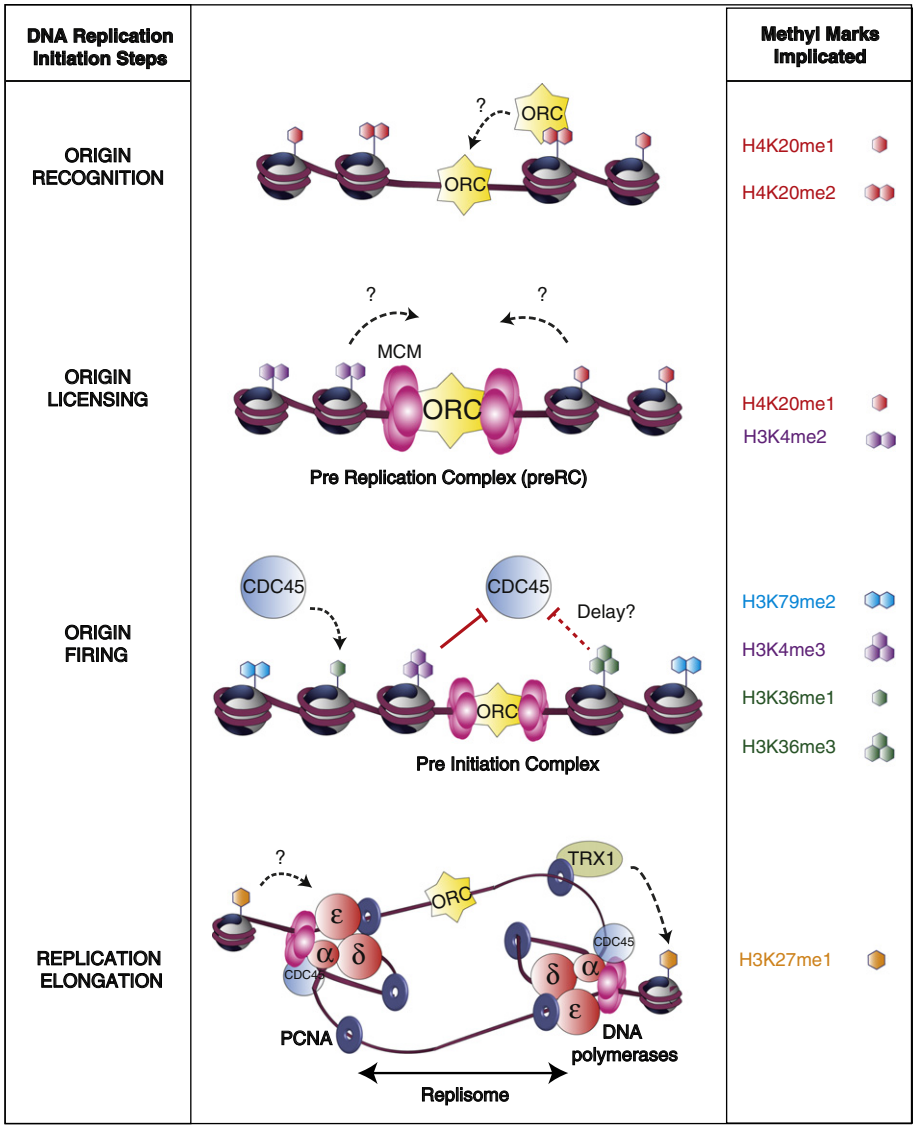

Fig. 1. Histone lysine methylation implicated in four phases of eukaryotic DNA replication. During the origin recognition step, H4K20me2 recruits ORC subunits to replication origins. For origin licensing, H4K20me1 is present at this stage, however, its role in promoting the assembly of the preRC remains unknown. In addition, H3K4me2 in yeast seems to be involved in this step. During origin firing, different methylation marks cooperate to regulate CDC45 binding to the pre-initiating complex. H3K36me1 likely recruits CDC45 whereas H3K36me3 may delay CDC45 loading, as this mark is found at late-replicating genes. H3K4me3 inhibits CDC45 binding. H3K79me2 is enriched during this phase, however its role remains unknown. Finally, TRX1 monomethylates H3K27 during elongation, however, the function of this mark remains elusive.

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