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Review

The many faces of histone H3K79 methylation

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ABSTRACT

Dot1/DOT1L (disruptor of telomeric silencing-1) is an evolutionarily conserved histone methyltransferase that methylates lysine 79 located within the globular domain of histone H3. Dot1 was initially identified by a genetic screen as a disruptor of telomeric silencing in *Saccharomyces cerevisiae*; further, it is the only known non-SET domain containing histone methyltransferase. Methylation of H3K79 is involved in the regulation of telomeric silencing, cellular development, cell-cycle checkpoint, DNA repair, and regulation of transcription. hDot1L-mediated H3K79 methylation appears to have a crucial role in transformation as well as disease progression in leukemias involving several oncogenic fusion proteins. This review summarizes the multiple functions of Dot1/hDOT1L in a range of cellular processes.

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1. Introduction

Genetic information within the eukaryotic cell nucleus is organized in a highly conserved DNA–protein complex, the chromatin, which supports and controls the vital functions of the genome. The basic unit of chromatin is the nucleosome, which contains 146 bp of DNA wrapped around a histone octamer containing two copies each of H2A, H2B, H3, and H4 [1]. The basic organization of the eukaryotic genome into chromatin impedes the protein factor accessibility required for gene transcription, DNA replication, recombination, and repair. Therefore, the cell has developed various mechanisms by which the chromatin structure can be regulated to increase access to DNA. These include adenosine triphosphate (ATP)-dependent chromatin remodeling, incorporation of histone variants into nucleosomes, and covalent histone modifications. [2–4] Histone modifications can alter the charge of specific residues, affecting the histone–histone and histone–DNA interactions, and can act as signals to create landing platforms for a diverse array of transcription factors, chromatin remodelers, and DNA-interacting proteins, which drive distinct downstream functions [1,4]. Histone modifications are highly regulated within the cell, and any misregulation is often associated with cancer and other physiological disorders [5]. Among the various known histone modifications, histone methylation has attracted much attention due to its diverse functions, which include transcriptional regulation, heterochromatin formation,

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X-chromosome inactivation, DNA repair, and cellular differentiation [1]. Histone methylation is carried out by histone methyltransferases (HMTs), which covalently modify specific lysine and arginine residues by transferring methyl groups from *S*-adenosyl-L-methionine. HMTs fall into two groups based on an evolutionarily conserved catalytic SET domain named after SU(var), Enhancer of Zeste, and Trithorax, the first three proteins identified to harbor this domain in *Drosophila* [6]. Disruptor of telomeric silencing-1 (hDot1L), which methylates lysine 79 located within the globular domain of histone H3, is unusual as it does not possess a SET domain. Dot1 is involved in a number of key processes ranging from gene expression to DNA-damage response and cell-cycle progression (Fig. 1). This review summarizes the diverse biological functions of Dot1 in various cellular processes [1].

1.1. Dot1 as a Methyltransferase

Dot1 (also known as *KMT4*) is an evolutionarily conserved enzyme that catalyzes the methylation of histone H3 at lysine 79. It was initially discovered as a gene that disrupts telomeric silencing when overexpressed [7]. Dot1 is the sole enzyme responsible for all forms of H3K79 methylation (monomethylation, dimethylation, and trimethylation) in *Saccharomyces cerevisiae*,*Drosophila melanogaster*, and humans, based on the fact that knockout of its gene in these organisms results in complete loss of H3K79 methylation [8]. The protein is conserved in mammals, called Dot1-like protein (DOT1L), and displays enzymatic properties similar to that of its yeast homologue. Dot1 is unique in being the only non-*SET* domain containing methyltransferase identified to date [8–10]. Two features of this enzyme distinguish it from other known HMTs. First, Dot1 requires a chromatin substrate, and is not active on free histones. Second, the lysine residue modification occurs within the globular region of histone H3, away from the usual histone modification sites that are located in the N- and C-terminal domains. H3K79 is located in the globular domain of histone H3, but it is exposed on the nucleosome surface where it can be methylated by DOT1L. However, this methylation occurs only in a nucleosomal context that is suggestive of a cross talk between H3K79 methylation and other histone modifications [10,11]. Studies regarding activity and regulation of Dot1 in many organisms have revealed roles in different biological processes such as transcription, cell-cycle regulation, and DNA damage response [12].

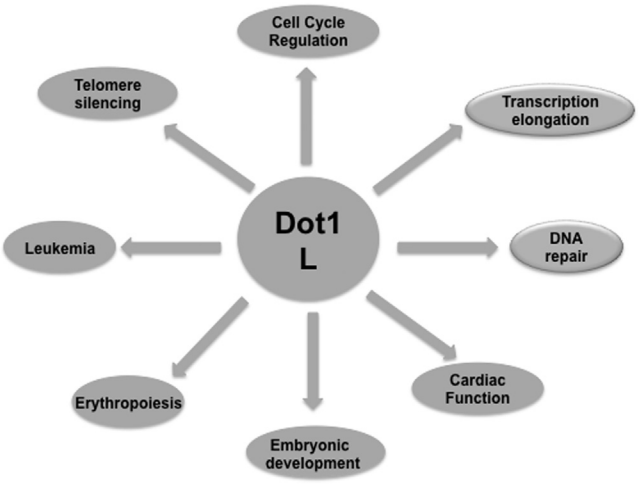

Fig. 1. Role of hDot1L in various cellular processes: hDot1L is involved in diverse cellular processes such as transcription elongation, DNA repair, cell-cycle regulation, and telomere silencing.

1.2. Cross talk between histone modifications in regulation of H3K79 methylation

For more than a decade now, chromosomal modifications have been noted to act in concert with each other in a context-dependent manner, which can lead to activation or repression of chromatin-mediated processes. This concept forms the basis of the *cross talk* between different modifications [13]. The inability of Dot1 to methylate free histone H3 suggests that trans-histone cross talk may regulate Dot1 activity. In yeast, histone H2B is monoubiquitinated at K123 by Rad6 ubiquitin-conjugating E2 enzyme and Bre1 ubiquitin E3 ligase. Both H2B-K123 and H3K79 are located close to each other on the nucleosome surface; further, the interplay between methylation of H3K79 and ubiquitination of H2B-K123 has been suggested because Rad6 (ubiquitin-conjugating enzyme) deletion was found to prevent H3K4 and H3K79 methylation [14–16]. Moreover, mutagenesis of H2B-K123 results in remarkable loss of these two methylations. These results indicate that H2B-K123 ubiquitination is a prerequisite for H3K4 and H3K79 methylation. This effect has been observed to be unidirectional, as Dot1 deletion has no effect on H2B-K123 ubiquitination [16]. Another histone cross-talk pathway that regulates H3K79 methylation levels in *S. cerevisiae* is the interaction of Dot1 with a short basic patch region of the histone H4 N-terminal tail. Sir3 and Dot1 compete for the same site on histone H4, and the acetylation of H4K16 blocks Sir3 binding and stimulates Dot1 binding and subsequent H3K79 methylation [17].

1.3. H3K79 methylation in transcriptional regulation

Gene expression in higher eukaryotes is intimately linked to DNA accessibility. Normally, DNA remains packaged into a condensed chromatin state inaccessible to the transcriptional machinery. Therefore, for transcription to occur, this state has to be changed by opening up of the chromatin structure. Histone-modifying enzymes are one of the major mediators of this process. Histone-modifying enzymes are targeted to their histone substrates by DNA-bound modulators (activators or repressors). The choice of the particular modulator depends on the given enzyme and the subsequent modification that it performs [3,4]. H3K79 methylation levels show strong correlation with transcriptional activity. In *S. cerevisiae*, Dot1 and H3K79 trimethylation has been detected in the transcribed regions of active genes [18–20]. In humans, ChIP–chip (chromatin immunoprecipitation coupled with gene expression microarrays) studies demonstrated that H3K79me2/me3 methylation is strongly correlated with gene activity. In *Drosophila*, ChIP–chip analysis also revealed a correlation between H3K79me2 and active gene transcription [21]. Mutations in the *Drosophila* Dot1 ortholog *grappa* lead to *polycomb* and *trithorax group* phenotypes, suggesting that H3K79 methylation may influence developmentally regulated gene expression in multicellular eukaryotes [22]. Furthermore, Steger et al. found that H3K79 methylation is linked to gene transcription in mice [23]. In human cells, ChIP–seq (chromatin immunoprecipitation coupled with deep sequencing) experiments indicated that H3K79 methylation is enriched at the transcribed genes [24]. Furthermore, H3K79 methylation is enriched on the histone variant H3.3, which is found at the transcriptionally active loci in *Drosophila* and mammals [25,26]. Dot1 has also been identified in RNA polymerase II- associated transcription elongation complexes. More recently, DOT1L was found in a complex in *Drosophila* with members of the Wnt pathway such as AF10, AF17, and AF9. Although P-TEFb was absent from this complex, Dot1L was still required for Wingless target gene expression [27–29]. Furthermore, the Moazed Lab showed that the SIR complex, which mediates the inhibition of transcription from reconstituted