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Review

Histone arginine methylation

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ABSTRACT

Arginine methylation is a common posttranslational modification (PTM). This type of PTM occurs on both nuclear and cytoplasmic proteins, and is particularly abundant on shuttling proteins. In this review, we will focus on one aspect of this PTM: the diverse roles that arginine methylation of the core histone tails play in regulating chromatin function. A family of nine protein arginine methyltransferases (PRMTs) catalyze methylation reactions, and a subset target histones. Importantly, arginine methylation of histone tails can promote or prevent the docking of key transcriptional effector molecules, thus playing a central role in the orchestration of the histone code.

1. Arginine methylation

The mammalian family of protein arginine methyltransferases (PRMTs) has nine members. These enzymes transfer a methyl group from S-adenosylmethionine (AdoMet) to a guanidino nitrogen of arginine resulting in S-adenosylhomocysteine (AdoHcy) and methylarginine. The PRMT family of AdoMet-dependent methyltransferases harbor a set of four conserved signature amino acid sequence motifs (I, post-I, II, and III), and a THW loop [1]. Motifs I, post-I, and the THW loop form part of the AdoMet-binding pocket [2]. There are three main forms of methylated arginine identified in mammalian cells: monomethylarginines (MMA); asymmetric dimethylarginines (ADMA); and symmetric dimethylarginines (SDMA). PRMTs are classified as either type I, type II, or type III, enzymes, which methylate the terminal (or ω) guanidino nitrogen atoms of arginine. Type IV enzyme activity catalyzes the monomethylation of the internal guanidine nitrogen atom and this type of activity has only been described in yeast. Type I and type II enzymes catalyze the formation of an MMA intermediate, then type I PRMTs (PRMT1, 2, 3, 4, 6, and 8) further catalyze the production of ADMA, while type II PRMTs (PRMT5 and 7) catalyze the formation of SDMA (Fig. 1A). Certain substrates are only monomethylated by PRMT7, which is referred to as type III enzymatic activity. Histone tails are a prime target for this family of enzymes (Fig. 1B).

2. Mammalian arginine methyltransferases

2.1. Prmt1

PRMT1 was the first mammalian protein arginine methyltransferase identified [3], and it is also responsible for the bulk (about 85%) of total protein arginine methylation activity [4]. The central role that PRMT1 plays as a diverse regulator of protein function is revealed by the disruption of this enzyme in mice, which die shortly after implantation [5]. PRMT1 displays wide substrate specificity, with a preference for methylating arginine residues that are flanked by one or more glycine residues – motifs often referred to as GAR sequences (Glycine and Arginine Rich) [6,7]. The three-dimensional structure of PRMT1 reveals that it is active as a homodimer [8]. PRMT1 also methylates histone H4 at arginine 3, generating the H4R3me2a mark [9], and thus contributing to the histone code. This modification on histone H4 functions as a transcriptional activation mark, which can recruit methyl-binding proteins and influence the deposition of other posttranslational marks in the vicinity. As a transcriptional coactivator, PRMT1 is recruited to promoters by a number of different transcription factors [10].

2.2. Prmt2

PRMT2 harbors a methyltransferase domain and a SH3 domain [11]. The SH3 domain binds the PRMT8 N-terminal domain and may also target it to substrates [12]. Initially, it was not believed to possess methyltransferase activity. However, recently very weak Type I activity was eked out of this enzyme [13]. PRMT2 can

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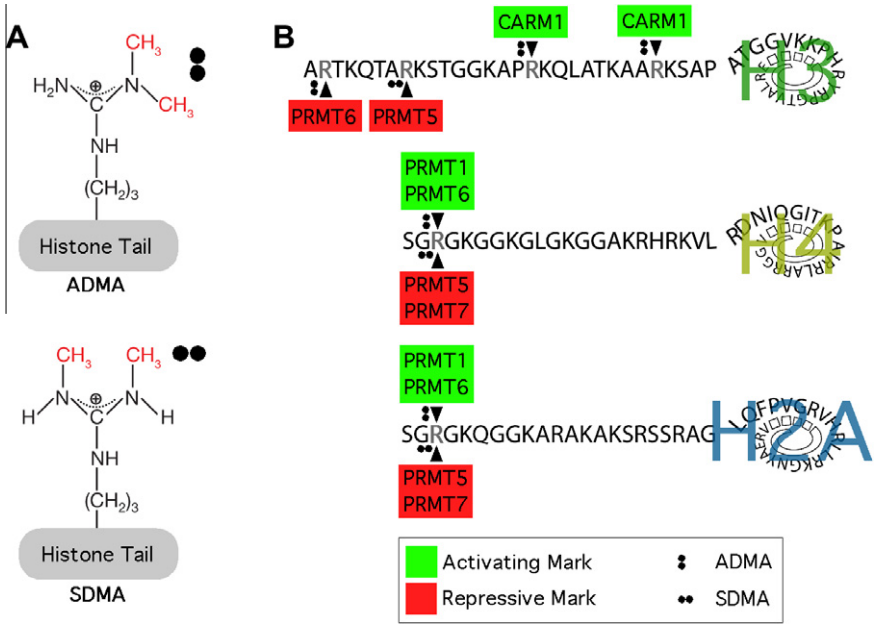

Fig. 1. Types and sites of histone tail arginine methylation. (A) Arginine residues in the tails of histones can be monomethylarginines (MMA), asymmetric dimethylarginines (ADMA), and symmetric dimethylarginines (SDMA). The MMA form of arginine is generally regarded as an intermediate on its way to the dimethylated state and is not depicted here. (B) The known sites of histone H3, H4, and H2A arginine dimethylation are shown. Red denotes transcriptional repressor activity and green denotes transcriptional activator activity.

methylate histone H4, although the site of methylation has not been mapped. PRMT2 is a coactivator of gene expression much like PRMT1 and CARM1, and this activity appears to rely upon the integrity of the methyltransferase domain. PRMT2 is a coactivator of both the androgen receptor and the estrogen receptor alpha [14,15]. In addition, PRMT2 can promote apoptosis and inhibit NF-kappaB function by blocking IkappaB-alpha nuclear export [16]. PRMT2 null mice are viable and grossly normal [17].

2.3. Prmt3

PRMT3 harbors a zinc-finger domain at its N-terminus, which is the substrate recognition module of this enzyme [18,19]. The 40S ribosomal protein S2 (rpS2) is a zinc-finger dependent substrate of mammalian PRMT3 [20]. Importantly, in fission yeast PRMT3 (called Rmt3) also methylates rpS2 [21], emphasizing the conserved nature of this enzyme/substrate pairing. In yeast, loss of PRMT3 results in a ribosomal subunit imbalance, which can be restored with the expression of a catalytic inactive mutant [22]. Mouse embryos with a targeted disruption of PRMT3 are small in size, but survive after birth and attain a normal size in adulthood. In these null mice, rpS2 is hypomethylated, demonstrating that it is an in vivo PRMT3 substrate [23]. PRMT3 seems to be located exclusively in the cytosol, thus it may not directly impact epigenetic pathways.

2.4. Carm1 (prmt4)

CARM1, which is also referred to as PRMT4, was identified as a steroid receptor coactivator and provided the first evidence that arginine methylation regulates transcription [24]. The recruitment of CARM1 to transcriptional promoters results in the methylation of histone H3 (H3R17me2a and H3R26me2a) and transcriptional regulators [10]. CARM1 is not only a steroid receptor coactivator, but it also reinforces other transcription factor pathways [10]. In addition, CARM1 methylates splicing factors and regulates the coupling of transcription and splicing [25]. CARM1 and PRMT1 do not share substrates [7]. CARM1 null mice die just after birth and are smaller than their wild-type littermates [26]. Further analysis of these null mice have revealed key in vivo roles for CARM1 in early T cell development [27], in adipocyte differentiation [28], in chondrocyte proliferation [29], and in the proliferation and differentiation of pulmonary epithelial cells [30]. CARM1 requires its enzymatic activity for all of its known in vivo functions [31].

2.5. Prmt5

PRMT5 is the predominant Type II arginine methyltransferase in mammals and is generally regarded as a strong transcriptional repressor [32]. It was first identified as a Jak2-binding protein and shown to methylate histones H2A, H3, and H4 [33,34]. In the nucleus, PRMT5 binds to COPR5 (cooperator of PRMT5), which appears to be responsible for its transcriptional corepressor activities. The COPR5 interaction alters the specificity of PRMT5, causing it to preferentially methylate H4R3 over H3R8 [35]. PRMT5 is recruited by numerous transcription factors and repressor complexes, including Snail [36], ZNF224 [37], Ski [38], and at the globin locus [39]. In the cytoplasm, PRMT5 is involved in snRNP biogenesis through its ability to methylate a number of Sm proteins [40,41], and it also methylates Piwi proteins, which regulate a class of small non-coding RNAs [42]. It should be noted that αFLAG M2-agarose enriches for PRMT5 activity [43], thus many affinity purified FLAG-tagged complexes are "contaminated" with PRMT5, confounding the field.

2.6. Prmt6

PRMT6 is predominantly localized to the nucleus and like PRMT1 methylates GAR motifs [44]. It is the primary enzyme responsible for H3R2 methylation in mammalian cells, [45–47]. H3R2 methylation, by PRMT6, counteracts the H3K4me3 activation mark, making it a transcriptional repressor. Thrombospondin-1 (TSP-1) is the first characterized transcriptionally repressed target of PRMT6 [48]. The general assumption that PRMT6 functions as a