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# Structural dynamics of protein lysine methylation and demethylation

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**Abstract**

Lysine methylation plays a central role in the "histone code" that regulates chromatin structure, impacts transcription, and responds to DNA damage. A single lysine can be mono-, di-, tri-methylated, or unmethylated, with different functional consequences for each of the four forms. This review (written in the early 2006) described structural aspects of methylation of histone lysine residues by two enzyme families with entirely different structural scaffolding (the SET proteins and Dot1p), and the protein motifs that recognize (decode) these methyl-lysine signals. We also discuss the recently discovered protein lysine demethylating enzymes (LSD1 and JmjC domains).
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## 1. Introduction

AdoMet-dependent MTases are involved in biosynthesis, signal transduction, protein repair, chromatin regulation, and gene silencing. Methylation substrates range in size from arsenite through DNA and proteins, and the atomic targets can be carbon, oxygen, nitrogen, sulfur, or even halides. Histones can be modified in many ways that affect gene expression, including acetylation, phosphorylation, ubiquitination, methylation, and sumoylation [1–3]. Evidence accumulated over the past few years suggests that such modifications constitute a "histone code" that directs a variety of processes involving chromatin [4–13]. For example, one chromatin modification, the phosphorylation of histone H2A, links the recruitment of histone modifiers and ATP-dependent chromatin-remodelling complexes to sites of DNA damage [14]. There are currently many known sites of lysine and arginine methylation on histones, and additional sites of modification are still being uncovered. Methylation at these sites, in combination with other modifications (or demodifications) at nearby residues, generates "modification cassettes" [15,16] that yield distinct patterns on chromatin for signaling downstream events [17]. The best-characterized sites of histone methylation are located on the N-terminal tails of histones (such as at Lys-4 and Lys-9 of histone H3 and Arg-3 of histone H4) that protrude from the nucleosome. In contrast, Lys-79 of histone H3 is located in the core of the histone, exposed on the nucleosome disk surface. The protein arginine methylation has been recently reviewed extensively in book chapters [18–20], and therefore in this review, we focus on progresses in the structural studies of histone lysine methylation enzymes,

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methyl-lysine recognition domains and methyl-lysine demethylases.

### 1.1. SET domain proteins

With one exception (Dot1p, see below), histone lysine (K) methyltransferases (HKMTs) contain a SET domain of approximately 130 amino acids. The SET domain was originally identified in three *Drosophila* genes involved in epigenetic processes, the suppressor of position-effect variegation 3–9, Su(var)3–9; an enhancer of the eye color mutant zeste, En(zeste); and the homeotic gene regulator Trithorax [21]. Mammalian homologues of *Drosophila* Su(var) 3–9 were the first HKMTs identified, and they specifically methylate H3 at Lys-9 [22]. So far, SET-containing HKMTs that methylate Lys-4, -9, -27, or -36 of histone H3 and Lys-20 of histone H4 have been identified. The SET domain is found in a large number of eukaryotic proteins (see pfam database) as well as in a few bacterial proteins [23] and is not limited to HKMTs. HKMTs can be classified according to the presence or absence and the nature of sequences surrounding the SET domain that are conserved within families [24,25]. Representatives of the major families include SUV, SET1, SET2, EZ, and RIZ (for example, see [26]). The SET7/9 and SET8 proteins do not fit into these families. The SUV family includes the greatest number of HKMTs.

### 1.2. Structures of SET domain proteins

Currently known structures of SET proteins include the crystal structures of two SUV family proteins, *Neurospora crassa* DIM-5 [23,27] (Fig. 1A) and *Schizosaccharomyces pombe* Clr4 [28] (Fig. 1B); six human SET7/9 structures in various configurations [29–34] (Fig. 1C); two human SET8 (or Pr-SET7) structures [35,36] (Fig. 1D); an NMR structure of a viral protein that contains only the SET domain (vSET) [37]; and a non-histone Rubisco MTase [38,39]. These structures revealed that the SET domain forms a novel β-fold with a series of curved β-strands forming several small sheets, packed together with post-SET, pre-SET, or an additional domain (i-SET) inserted into SET domain.

### 1.3. The SET domain forms a knot-like active site

The SET domain folds into several small β-sheets that surround a knot-like structure by threading a C terminus through an opening of a short loop formed by a preceding stretch of the sequence (Figs. 1A–D and 2A). This remarkable knot-like structure brings together the two most-conserved SET signature motifs, RFINH×C×PN (III) and EL×FDY (IV) (Fig. 2B), of the SET domain to form an active site in a location immediately next to the methyl-donor-binding pocket and peptide-binding

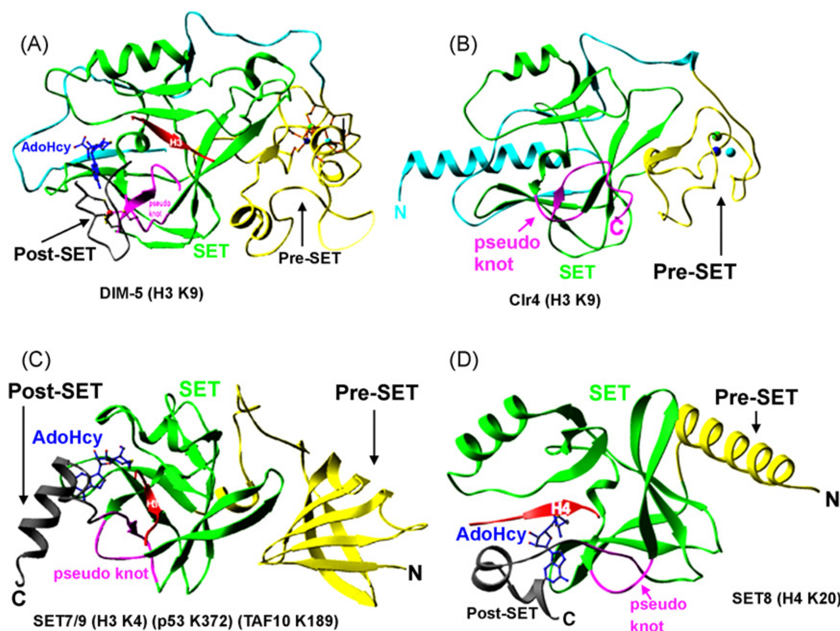


Fig. 1. SET domain protein (histone) lysine MTase structures. (A) Ribbon diagram of DIM-5 protein (one of the smallest members of the SUV family) contains four segments: a weakly conserved N-terminal region (cyan), a pre-SET domain containing nine invariant cysteines (yellow), the SET region containing four signature motifs (green and magenta), and the post-SET domain containing three invariant cysteines (grey); (B) *S. pombe* Clr4; (C) human SET7/9; (D) human SET8 (or PR-SET7).

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