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Review article

Methyllysine binding domains: Structural insight and small molecule probe development

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A frequent posttranslational modification that regulates gene expression is the mono-, di-, and/or tri-methylation of lysine residues on the histone tails of chromatin. The recognition of methylated lysine marks is facilitated by specific reader proteins that contain a methyllysine binding domain. This class of reader proteins has emerged as a focus of epigenetic research due to its crucial role in gene regulation, oncogenesis and other disease pathways. The design and synthesis of small molecules that target these domains and disrupt reader/histone protein-protein interactions have demonstrated the druggability of methyllysine binding pockets and provided preliminary evidence that their disruption holds therapeutic potential. In this review, we detail the structures of methyllysine binding domains, highlight the primary roles of these reader proteins in both normal and disease states, and describe the current status of small molecule development against these emerging epigenetic regulators.

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Abbreviations

PTMs	Posttranslational modifications
Kme0	non-methylated lysine
Kme1	monomethylated lysine
Kme2	dimethylated lysine
Kme3	trimethylated lysine
MBT	Malignant brain tumor
PWWP	proline-tryptophan-tryptophan-proline
Chromodomains	chromatin organization modifier domains
l(3)mbt	Lethal (3) malignant brain tumor
PHD	plant homeodomain fingers
dSCM	Sex Comb Midleg
dSGMBT	SCM-related gene containing four MBT domains
Rb	retinoblastoma
VS	Virtual screen
FP	Fluorescence polarization
ITC	Isothermal titration calorimetry
53BP1	p53-binding protein 1
FRAP	Fluorescence recovery after photo-bleaching
BCLAF1	BCL2-associated transcription factor 1
DSBs	Double-strand breaks
ATM	Ataxia telangiectasia mutated
BRCA1	Breast cancer susceptible gene 1
FACS	Fluorescence-activated cell sorting
CSR	Class switch recombination
HP1	Heterochromatin-associated protein 1
PcG	Polycomb group
CHD	Chromo helicase DNA-binding
CBX	Chromobox
CDY	Chromodomain Y chromosome
FITC	Fluorescein isothiocyanate
Dnmt3a	DNA methyltransferase 3a
HDGF	Hepatoma-derived growth factor
HATH	Homologous to Amino Terminus of HDGF
JARID1A	Jumonji, AT-rich interactive domain 1A
AML	Acute myeloid leukemia
ARD	Armadillo repeat domain
PRC2	Polycomb repressive complex 2
BLS	Bare lymphocyte syndrome
RFXANK	Regulatory factor X associated ankyrin containing protein
GLP	G9a-like protein
ADD	ATRX-DNMT3-DNMT3L

1. Introduction

The basic unit of chromatin is the nucleosome, which is composed of 146 base pairs of DNA wrapped around an octamer of four histone molecules (2 each of H2A, H2B, H3, and H4). Chromatin exists in either a condensed state (heterochromatin), in which nucleosomes are tightly packed and gene expression is repressed, or a relaxed state (euchromatin) where gene expression is activated [1]. Direct posttranslational modifications (PTMs) to histones can influence chromatin structure and play a primary role in modulating chromatin state and the resulting levels of gene expression/repression. These modifications can also be inherited by daughter cells to maintain lineage specific transcription profiles [2]. In general, histone PTMs are reversible and are characterized by the covalent addition of a functional group to the side chain of a specific amino acid residue on the histone tail. Common histone PTMs include acetylation, ubiquitination, or methylation of lysine residues and methylation of arginine residues. Depending on the functional group attached and the specific residue affected, the ultimate result of histone PTMs can be either gene expression or repression [3–7].

One of the most frequent histone PTMs is the mono-, di- and trimethylation of lysine residues (Kme1-3). The dynamic methylation state of histone lysine residues is controlled by a balance in the activity of lysine methyltransferases ('writers'), which transfer methyl groups from *S*-adenosylmethionine to the lysine residue, and demethylases ('erasers'), which remove methyl groups [3]. Lysine methylation results in the recruitment of a variety of proteins known as 'readers' that recognize and bind to the methyllysine residue. These reader proteins recruit other effector proteins to form a multi-protein complex and subsequently guide transcriptional expression or repression, depending on the specific residue affected. The conserved recognition of methyllysine marks by reader proteins is largely determined by the interaction between the methylammonium group and aromatic residues in the binding pocket of reader proteins, which form an aromatic cage around the methylated residue. Depending on the reader, the aromatic cage can contain 1-4 aromatic residues that bind to one or multiple methylation states. One exception is the ADD domain of ATRX whose mode of recognition is accomplished through polar residues that non-conventionally bind to its marks [8–10]. Because methylated lysines (Kme1, Kme2 and Kme3) vary in their size, distribution of positive charge, hydrophobicity and ability to donate hydrogen bonds, readers are able to selectively bind to specific marks primarily through cation-π interactions (Fig. 1) [11].

In addition, structural studies have demonstrated that methyl binding proteins that prefer a lower methylation state (Kme1 or Kme2) primarily use a cavity-insertion recognition mode by which the Kme side chain is buried within a deep cleft (Fig. 2A) while those that favor higher methylation states (Kme2 and Kme3) use a surface groove recognition mode (Fig. 2B). Notably, there are exceptions to the cavity-insertion and surface recognition modes. For instance, PHD type domains use surface groove recognition to read all methylated lysine marks (Kme0/1/2/3) [8,12]. As expected, steric repulsion plays a larger role in the cavity-insertion recognition mode while the wider methyllysine binding pocket of surface grove recognition mode allows for the binding of higher methylation states. In addition, for some methyllysine binding domains a nearby

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