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On your histone mark, SET, methylate!

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Lysine methylation of histones and non-histone proteins has emerged in recent years as a posttranslational modification with wide-ranging cellular implications beyond epigenetic regulation. The molecular interactions between lysine methyltransferases and their substrates appear to be regulated by posttranslational modifications surrounding the lysine methyl acceptor. Two very interesting examples of this cross-talk between methyl-lysine sites are found in the SET [Su(var)3–9, Enhancer-of-zeste, Trithorax] domain-containing lysine methyltransferases SET7 and SETDB1, whereby the histone H3 trimethylated on lysine 4 (H3K4^{me3}) modification prevents methylation by SETDB1 on H3 lysine 9 (H3K9) and the histone H3 trimethylated on lysine 9 (H3K9^{me3}) modification prevents methylation by SET7 on H3K4. A similar cross-talk between posttranslational modifications regulates the functions of non-histone proteins such as the tumor suppressor p53 and the DNA methyltransferase DNMT1. Herein, in cis effects of acetylation, phosphorylation, as well as arginine and lysine methylation on lysine methylation events will be discussed.

Introduction

The genome of eukaryotic organisms is laid down on a proteinaceous foundation, the histone octamer, and wrapped around it to form the basic unit of chromatin, the nucleosome. This is basically how eukaryotes achieve to compact and facilitate the organization of the genome within the confines of the nucleus and temporally control the access to genetic elements. The nucleosome is composed of genomic DNA as well as two copies of each of the four canonical histones, H2A, H2B, H3 and H4. The access to genetic elements is regulated by various enzymatic activities including histone posttranslational modifications, chromatin remodeling and histone exchange by histone variants that alter the physical properties of the nucleosome or provide alternative sequences for posttranslational modifications and regulation.

Histone tails harbor multiple posttranslational modifications. Historically, it was proposed that these histone modifications could provide a code, termed appropriately the histone code,[1] which could dictate biological outcomes through protein-protein interactions with modification-specific binding proteins, broadly called readers. However, recent evidence suggests that a modification on the histone tail does not always lead to a predefined biological outcome, but depending on the context may even lead to opposite consequences. A notable paradigm involves the histone H3 trimethylated on lysine 4 (H3K4^{me3}) mark, which is usually associated with transcriptional activity as it is present at the transcriptional start site (TSS) of most expressed genes.[2] In the context of DNA damage responses, H3K4^{me3} is read by the plant homeodomain (PHD) of the inhibitor of growth 2 (ING2) tumor suppressor, leading to transcriptional silencing of cell cycle genes.[3,4] However, in response to genotoxic stress, H3K4^{me3} can also be read by ING4, which, through associated histone acetyltransferase activity, stimulates the transcription of cellular adhesion genes.[4,5] Thus, the broader term chromatin signaling has been gaining popularity.[6-8]

Lysine methyltransferases (KMTs) are fundamental players in the regulation of chromatin signaling. This is emphasized by several reports showing that KMTs functional defects can lead to cancer,[9,10] growth defects,[11] neurological disorders,[12] and other human pathologies. There are currently over 60 KMTs predicted in the latest human genome annotation. With the exception of DOT1L[13,14] and the WRAD complex,[15] most KMTs harbor a predicted SET domain, which catalyzes the transfer of a methyl group from S-adenosylmethionine to the ε-amine on the side chain of lysine residue. Although predicted a few years ago,[16] ten members of the seven β-strand methyltransferase-like (METTL) family were recently characterized as KMTs.[17] Unlike other posttranslational modifications, lysine methylation occurs in three different flavors. Specifically, lysines can either be unmodified (K), mono (K^{me1}), di (K^{me2}) or trimethylated (K^{me3}). These incremental methylation states have the potential to lead to diverse biological outcomes through readers. These include Ankyrin, Chromo, MBT (malignant brain tumor), PHD, PWWP (proline-tryptophan-Ttryptophan-proline), Tudor and WD40 domains.[18] The biological significance of aberrant chromatin signaling events is emphasized by the fact that several readers have clear links to cancer,[19-21] suggesting a central role for lysine methylation in maintaining cellular homeostasis and in preventing neoplastic diseases.

Specific histone modifications appear to dictate whether or not a KMT can further modify its substrate. SET domain-containing methyltransferases seem to be particularly sensitive to the sequence and posttranslational modifications surrounding the target lysine site. I will explore within this short review the cross-talk between cis lysine methylation sites and other adjacent posttranslational modifications within histones H3 (**Fig. 1**) and H4 as well as a few non-histone proteins.

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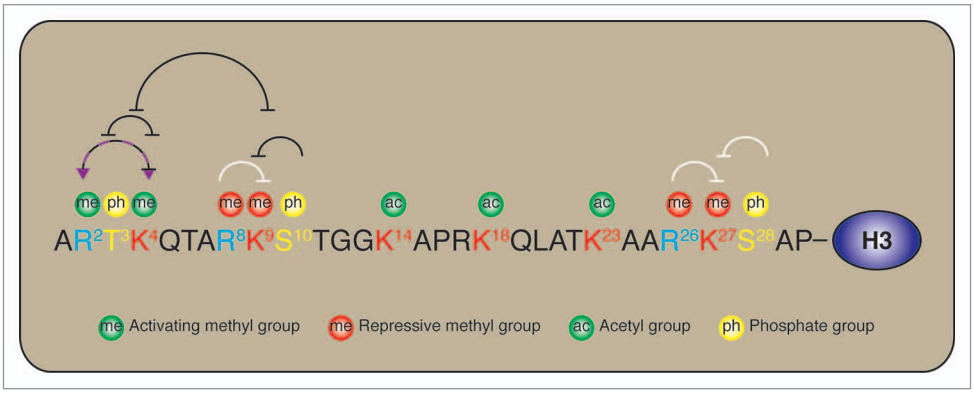

Figure 1. Cross-talk on histone H3 N-terminus. The amino acid sequence of the histone tail of H3 is annotated to highlight the position of key modified residues. Black lines represents published cross-talk events. White lines represent putative cross-talk events. The dashed black line between H3R2 and H3K4 represents the antagonistic cross-talk between H3R2^{me2a} and H3K4^{me3}. The purple arrows between H3R2 and H3K4 highlight the permissive cross-talk between H3R2^{me2s} and H3K4^{me3}.

Regulation of H3 Lysine 4 Methylation (H3K4^{me})

The mixed lineage leukemia (MLL) protein lysine methyltransferase complex is evolutionarily conserved and mediates the methylation of H3K4. Chromosomal translocations of *MLL* are commonly found in leukemias and lead to aberrant expression of developmental and hematopoietic genes. Other KMTs that modify H3K4 include SETD1A and SET7.[22] The H3K4^{me1} modification marks enhancers,[23] while H3K4^{me3} surrounds transcriptional start sites and positively correlates with gene expression.[2]

H3R2^{me2a} prevents H3K4^{me}. The asymmetric dimethylation of histone H3 arginine 2 (H3R2^{me2a}) by the protein arginine methyltransferase PRMT6 precludes the methylation of H3K4 by the ASH2L/WDR5-containing MLL methyltransferase complex by preventing the WD40 repeat-containing WDR5 subunit from interacting with H3.[24] The H3R2^{me2a} modification is conserved in *Saccharomyces cerevisiae*.[25] Interestingly, the H3R2^{me2a} mark was shown to associate genome-wide with silenced chromatin and to prevent methylation of H3K4 by the Set1 lysine methyltransferase.[25]

H3R2^{me2s} facilitates H3K4^{me}. The recently identified symmetrically dimethylated H3R2 (H3R2^{me2s}) histone mark is not only found to overlap genome-wide with H3K4^{me3} in mouse, but it is conserved in *Xenopus laevis*, *Drosophila melanogaster* and *Saccharomyces cerevisiae* and detected in cis with H3K4^{me3} on the same histone tail.[26] Interestingly, the methylation of H3R2 requires both H3K4^{me3} as well as H3K4.[26] The arginine methyltransferases PRMT5 and PRMT7 were recently found to catalyze the formation of H3R2^{me2s}.[27] Unlike the asymmetrically dimethylated form, H3R2^{me2s} facilitates the interaction between H3 and the MLL complex subunit WDR5.[27] Thus, by enhancing MLL association with H3, WDR5 presumably facilitates H3K4^{me3} on H3R2^{me2s} modified histones. Summarily, H3R2^{me2s} facilitates H3K4^{me3} and conversely, H3K4^{me3} facilitates H3R2^{me2s}.

H3T3^{ph} prevents H3K4^{me3}. The trimethylation of H3K4 prevents H3 phosphorylation on tyrosine 3 (H3T3ph) by haspin.[28] Interestingly, the opposite cross-talk effect was also be observed by H3T3^{ph} on H3K4 methylation by MLL1.[29] Specifically, H3T3 is inserted in a defined structure within MLL1 SET domain.[29] The bulky and negatively charged phosphate group on H3T3^{ph} would hypothetically lead to the repositioning of the threonine and likely change the orientation of the neighboring target lysine, thereby impairing MLL1 activity on H3K4.[29]

H3K9$^{me2/3}$ prevents H3K4^{me1}. The SET7 lysine methyltransferase monomethylates the histone H3 on lysine 4 (H3K4^{me1}), but also modifies non-histone proteins including the tumor suppressors p53[30] and pRB,[31] the hormone-responsive transcription factors estrogen receptor α (ERα)[32] and androgen receptor (AR),[33] the DNA methyltransferase DNMT1,[34] the histone deacetylase SIRT1,[35] as well as several other non-histone proteins.

Interestingly, SET7 has weaker activity on a H3K9^{me2} peptide relatively to the unmodified H3 peptide.[22] In addition, premethylation of H3 on K9 by the methyltransferase SUV39H1, which catalyzes the formation of H3K9^{me3}, impaired SET7-dependent methylation on H3K4.[22] The crystal structure of H3-bound SET7 suggests that K9 from H3 is oriented toward the glutamic acid 271 (E271) of SET7. H3K9 and SET7E271 are presumably making electrostatic interactions.[36] Thus, H3K9^{me3} may affect these intermolecular interactions, preventing SET7 from methylating H3K4.

The mammalian homolog of the *Drosophila melanogaster* Trithorax group (TrxG) protein Ash1, ASH1L is a lysine methyltransferase that methylates histone H3 on possibly several sites, but is associated with active transcription.[37] Interestingly, the methylation activity of ASH1L on H3K4 is impaired by H3K9^{me3}.[37] However, there is no structural evidence available to suggest a possible mechanism that could explain how H3K9^{me3} impairs ASH1L-mediated methylation of H3K4.

Biological consequences of H3K4^{me3} cross-talk. The presence of H3R2^{me2a} in the body of genes and TSS prevents the deposition of H3K4^{me3} at silenced genes.[24] The absence of H3R2^{me2} and the presence of H3R2^{me2} at the TSS of actively transcribed genes facilitate the association of WDR5 with nucleosomes, thereby allowing trimethylation of H3K4.[27] Upon cell cycle arrest, the promoters of several transcriptional regulator genes are enriched with the H3R2^{me2} mark.[27] Although global levels of WDR5

are diminished in growth arrested cells, WDR5 is enriched at H3R2^{me2}-marked promoters.[27]

The H3R2^{me2s} mark enhances the affinity of the RAG2 PHD domain for H3K4^{me3} by 20-fold.[26] Thus, the cross-talk between H3R2^{me2} and H3K4^{me3} possibly controls V(D)J recombination events mediated by RAG2 by enhancing the association of RAG2 at dually modified H3R2^{me2}K4^{me3} chromatin loci, such as antigen receptor genes.

The MLL complex subunit Ash2L stimulates transcription that is driven by the TBP-associated factor TAF3 through methylation of H3K4 and thereby enhancing the interaction between H3K4^{me3} and the PHD domain of TAF3.[38] However, upon phosphorylation of H3T3 by haspin, Ash2L fails to stimulate TAF3-activated transcription.[39] In addition, H3T3 phosphorylation by haspin during mitosis is essential for proper alignment of metaphase chromosomes.[40] Hypothetically, phosphorylation of H3T3 by haspin during mitosis could prevent the deposition of H3K4^{me3} marks and the opening of condensed centromeric chromatin. Interestingly, pharmacological inhibition of haspin activity induces centrosome amplification, mitotic catastrophe and apoptosis.[41]

Regulation of H3 Lysine 9 Methylation (H3K9me)

First identified as an H3K9-specific methyltransferase in 2002,[42] SETDB1 modifies H3K9[43] and ING2 in vitro.[44] Interestingly, SETDB1 catalytic activity is enhanced by an ATPase, mAM, which allows SETDB1 to convert H3K9^{me2} to H3K9^{me3}.[45] There are several other H3K9-specific KMT, including SUV39H1,[46] SUV39H2[47] G9A,[48] and PRDM2.[49] Interestingly, G9A, GLP, SETDB1 and SUV39H1 form an enzymatic complex.[50] The H3K9^{me2} and H3K9^{me3} marks are enriched at the transcriptional start site of silenced genes, while H3K9^{me1} is found at transcribed promoters.[2]

H3K4^{me3} prevents H3K9^{me3}. Interestingly, the euchromatic mark H3K4^{me3} prevents methylation of H3K9 by SETDB1 as well as by the other H3K9-specific KMTs G9A and SUV39H1.[44] In vitro experimental approaches showed that H3K4^{me3} compromised methylation of H3K9 by SETDB1, G9A and SUV39H1.[44] Importantly, depletion of WDR82, an essential subunit of H3K4-specific KMT complexes,[51] led to severe reductions in H3K4$^{me2/3}$ levels and concomitant increase in H3K9^{me3} levels in vivo,[44] arguing that methylation on the H3K4 site could inherently preclude H3K9 methylation, providing a passive mechanism for the segregation of the euchromatic and heterochromatic marks H3K4^{me3} and H3K9^{me3}, respectively. It was independently reported that an un-specified methylation state of H3K4 impaired H3K9 methylation by SUV39H1 in vitro.[52]

The structure of G9A reveals that histone H3 lysine 4 is buried in an acidic fold comprising the aspartic acids D1074 and D1088,[53] suggesting that the aspartic acid residues would confer electrostatic interactions with the positively charged H3K4 and that methylation of H3K4 could interfere with those interactions. Indeed, G9A activity on H3 is lower on H3K4^{me3}, but the D1074A/D1088A G9A mutant has increased activity on H3K4^{me3} compared with the unmodified protein.[44] Hypothetically, the alanine mutations could provide additional space to accommodate the methyl groups of H3K4^{me3} into the acidic fold of G9A.

H3R8^{me} potential effect on H3K9^{me3}. The acetylation of H3K9 can prevent PRMT5 from methylating H3 arginine 8 (H3R8),[54] thus highlighting a potential cross-talk between H3R8^{me} and H3K9^{me}. Interestingly, the structure of G9A reveals that H3R8 is surrounded by three aspartic acids (D1074, D1078 and D1088) and that the amino groups on the side chain of H3R8 make electrostatic interactions with these three aspartic acid residues.[53] This acidic fold is shared by H3R8 and H3K9 where both H3 basic residues converge. The methylation of H3R8 by PRMT5 could undoubtedly sterically impede the proper insertion of H3 tail into the SET domain of G9A and prevent the methylation of H3K9.

H3S10^{ph} prevents H3K9^{me3}. Phosphorylation of H3 on serine 10 (H3S10ph) prevents methylation of H3K9 by G9A[55] and by SETDB1.[43] In addition, H3S10^{ph} severely impairs methylation of H3K9 by SUV39H1 in vitro.[46] According to H3-bound G9A structure,[53] the OH group on the side chain of H3S10 makes electrostatic interactions with the arginine 1214 of G9A. Thus, phosphorylation of H3S10 could destabilize this interaction and possibly lead to poor KMT-substrate association and decreased H3K9 methylation. However, H3S10^{ph} on already modified H3K9^{me3} does occur and is involved in regulating the association of the heterochromatin protein HP1 with H3K9^{me3}.[56,57] The impaired activity of G9A and SETDB1 on H3S10^{ph} suggests that either H3S10 is phosphorylated only after the methylation of H3K9 or that another KMT is responsible for the catalysis of H3K9^{me3}S10ph.

Biological consequences of H3K9^{me3} cross-talk. The H3S10^{ph} mark prevents subsequent methylation of H3K9, but also prohibits the binding of the HP1 proteins to H3K9^{me3}. Modulation of H3S10^{ph} level by inhibiting or silencing the Aurora B kinase enhanced the association of HP1 proteins with mitotic chromosomes, suggesting a mechanism for the dissociation of HP1 proteins from chromatin during the M phase of the cell cycle.[56]

Heterochromatin was proposed to be propagated via the association of HP1 proteins with H3K9^{me3}, allowing further H3K9 methylation by the HP1-associated methyltransferase SUV39H1.[58] The cross-talk between H3K4^{me3} and H3K9^{me3} could provide a complementary mechanism to prevent the propagation of silenced chromatin states into transcriptionally active regions and vice versa.

Regulation of H3 Lysine 27 Methylation (H3K27me)

Although H3K27 surrounding amino acid sequence (ARKSA) is very similar to H3K9 (ARKST), only EZH1[59] and EZH2[60] were reported to catalyze the methylation of H3K27. The monomethyled H3K27^{me1} mark is enriched at actively transcribed promoters whereas the trimethylated H3K27^{me3} mark is associated with silenced promoters.[2]

H3R26^{me} and H3S28^{ph} potential effect on H3K27^{me}. Although the H3-bound EZH2 structure has not been solved yet, it is tempting to speculate based on the aforementioned cross-talk between H3K4 and H3K9 that either methylation of

H3R26 by PRMT4[61] or phosphorylation of H3S28 by MSK1/2[62] could affect EZH2 association with H3 and its activity on H3K27. Mass spectrometric analysis detected the presence of H3S28^{ph} on monomethylated and dimethylated H3K27, but not on trimethylated H3K27 peptides,[63] suggesting that H3K27^{me3} and H3S28^{ph} are mutually exclusive modifications and that phosphorylation of H3S28 precludes the trimethylation of H3K27.

Regulation of H3 Lysine 79 Methylation (H3K79me)

H3T80^{ph} potential effect on H3K79^{me}. A few years ago the H3T80^{ph} modification was detected by mass spectrometric analysis,[64] opening the possibility that, similarly to the cross-talk between H3S10^{ph} and H3K9^{me3}, H3T80^{ph} could regulate the methylation of H3K79 by DOT1L. The crystal structure of the yeast ortholog of DOT1L, Dot1p, highlights an acidic cleft that could accommodate the basic charges surrounding H3K79, including R72 and R83.[65] Thus, the addition of a negatively charged phosphate group on H3S80 may affect the substrate-enzyme interaction. Indeed, the mutation of the acidic cleft of Dot1p abolished methyltransferase activity on H3K79.[65]

Regulation of H4 Lysine 20 Methylation (H4K20me)

H4K16^{ac} and H4K20^{me} are antagonistic marks. Lysine methylation at H4K20 prevents the acetylation of H4K16 by the acetyltransferase p300 in vitro.[66] Interestingly, the inverse cross-talk was also observed whereby the H4K16^{ac} mark prevents H4K20 methylation.[66] Although the H4K16^{ac} and H4K20^{mc} marks are mutually exclusive, the H4K12^{ac} mark was recently detected along with the novel H4K16^{me1} mark.[67] The structure of H4-bound SET8[68] reveals that H4K16 is surrounded by alanine 342 (A342), A346 and histidine 347 (H347), which are found at the carboxy terminal part of SET8 catalytic domain. The side chain of H347 makes hydrogen bonding with H4 peptide backbone.[68] In particular, the imidazole Nε2 atom of H347 and the backbone carbonyl of H4K16 are hydrogen bonding.[68] Thus, posttranslational modifications of H4K16 could alter these interactions and affect SET8 ability to methylate H4K20. Interestingly, an histidine to phenylalanine mutation at position 347 (H347F) led to increased substrate affinity.[68]

Biological consequences of H4K20^{me2} cross-talk. Interestingly, the silencing of the histone acetyltransferase TIP60 decreased H4K16^{ac} levels and induced the stabilization of 53BP1 association with H4K20^{me2} at DNA damage sites.[69] In addition, the inhibition of histone deacetylase activity by Trichostatin A led to enhanced H4K16^{ac} levels and concomitant reduction in 53BP1 association with chromatin at DNA damage foci.[69] The interaction of 53BP1 tandem tudor domain (53BP1$_{TT}$) with H4K20^{me2} is well-established.[70,71] However, the acetylation of lysine 16 on H4K20^{me2} reduced the affinity of 53BP1$_{TT}$ for the mark. The acetylated form of H4 likely disrupts electrostatic interactions between H4K16 and an acidic patch in 53BP1 tandem tudor domain (amino acids E1549, D1550 and E1551).[69] The cross-talk between H4K16^{ac} and H4K20^{me2} facilitates the dissociation of 53BP1 from chromatin at DNA damage breaks, allowing the recruitment of BRCA1 and homologous recombination repair.[69]

H2A and the H2A variant H2AZ. The dual modification H2AK5^{ac} K9^{me1} was recently detected by mass spectrometry.[67] Interestingly, H2AK5 aligns with H2AZK4 and H2AK9 aligns with H2AZK7. Both K4 and K7 on H2AZ were recently reported to be methylated by the methyltransferase SETD6.[72] However, acetylation and methylation of H2AZ are mutually exclusive modifications.[72] Given the similarities between the H2AK5K9 and H2AZK4K7 sequences, it seems likely that SETD6 could be responsible for the reported methylation of H2AK9.

Non-Histone Protein Substrates Cross-Talk

Tumor suppressor p53. The p53 tumor suppressor protein is methylated on at least four lysine residues. SMYD2 mono-methylates p53 on lysine K370 (p53K370^{me1}),[73,74] while SET7 monomethylates p53 on lysine K372 (p53K372^{me1})[30] in the regulatory domain. The p53K372^{me1} modification leads to p53-dependent transcriptional activation.[30] Interestingly, the SET7-mediated p53K372^{me1} modification prevents methylation by SMYD2 on K370 and repression of p53 activities.[73] However, the SMYD2-mediated methylation of p53, p53K370^{me1}, does not affect SET7 activity on p53.[73] The p53-bound SMYD2 structure was resolved and highlights several interactions between p53K372 and SMYD2 SET domain, including an hydrogen bond between p53K372 ε-amine group and the carbonyl of SMYD2 valine 215.[74] Therefore suggesting that p53K372^{me1} could sterically hinder the interaction of p53K372 with SMYD2 valine 215 and impair the methylation of K370 by SMYD2.[74]

The tumor suppressor is also dimethylated by the G9A and G9A-like KMT GLP on lysine 373 (p53K373^{me2}).[75] Interestingly, the aliphatic side chain of K373 from p53 is inserted within an aromatic cage of the SMYD2 catalytic domain that is lined by Y245, Y344, Y370 and Y374. The lysine K373 of p53 interacts directly with the side-chain of SMYD2Y344 through van der Waals interactions, whereas its ε-amine of p53K373 forms hydrogen bonds OH groups of Y370 and Y374.[74] Thus, G9A-mediated dimethylation of p53, p53K373^{me2}, could hypothetically increase interactions with SMYD2 aromatic cage, as seen with the cation-π interactions-mediated increased affinity between ING4$_{PHD}$ and H3K4^{me3},[5] and lead to methylation of p53 at K370. This cooperative cross-talk between the two marks would be logical as both p53K370^{me1} and p53K373^{me2} inactivate p53 functions.[73,75]

Similarly to histones, lysine methylation of p53 not only involves cross-talk between the different modifications, but also serves as docking sites for readers. Specifically, the recognition of p53K370^{me2} by 53BP1 has the consequence of activating p53-dependent transcription.[76] The DNA damaging agent adriamycine activates a p53-dependent response and induces the methylation of p53K372 by SET7.[30] Chromatin signaling events leading to the methylation of p53 at K372 by SET7 could potentially prevent the modification of K370 by SMYD2 and diminish the association between p53 and 53BP1.

The p53 protein is also monomethylated at K382 (p53K382^{me1}) by SET8.[77] In the context of DNA damage signaling induced by neocarzinostatin, the levels of p53K382^{me1} are reduced.[77] The methylation of p53 by SET8 leads to reduced p53-dependent expression of *p21*.[77] Interestingly, L3MBTL1 binds to p53K382^{me1} to silence the expression of *p21* under normal conditions, but upon induction of DNA damage, p53 is relieved from L3MBTL1.[78] Summarily, the p53K382^{me1} mark provides a docking site for the transcriptional silencer L3MBTL1 and upon genotoxic stress, reduced p53K382^{me1} level are relieving L3MBTL1 from p53, thereby allowing p53-dependent transcriptional activation. Interestingly, the dimethylated (p53K382^{me2}) form of p53 is induced by DNA damage and elicits the association with 53BP1.[79]

DNA methyltransferase DNMT1. The DNA methyltransferase DNMT1 is lysine monomethylated on K142 by SET7.[34] Interestingly, the phosphorylation of DNMT1 at serine 143 by AKT1 interferes with the methylation of K142.[80] The DNMT1-bound SET7 structure reveals a polar interaction between DNMT1 S143 and K317 as well as van der Waals contact with L267 of SET7.[80] Therefore, S143^{ph} should break the van der Waals contact with L267 and impair methylation of DNMT1K142.

Concluding Remark

It is an exciting era for the field of chromatin signaling. With each new posttranslational modification being characterized, new doors for potential cross-talk events and chromatin signaling networks open.

Disclosure of Potential Conflict of Interests

No potential conflicts of interest were disclosed.

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