Abstract. The field of cancer epigenetics has been evolving rapidly in recent decades. Epigenetic mechanisms include DNA methylation, histone modifications and microRNAs. Histone modifications are important markers of function and chromatin state. Aberrant histone methylation frequently occurs in tumor development and progression. Multiple studies have identified that histone lysine methyltransferases regulate gene transcription through the methylation of histone, which affects cell proliferation and differentiation, cell migration and invasion, and other biological characteristics. Histones have variant lysine sites for different levels of methylation, catalyzed by different lysine methyltransferases, which have numerous effects on human cancers. The present review focused on the most recent advances, described the key function sites of histone lysine methyltransferases, integrated significant quantities of data to introduce several compelling histone lysine methyltransferases in various types of human cancers, summarized their role in tumor development and discussed their potential mechanisms of action.

Contents

1. Introduction
2. Histone lysine methyltransferases
3. Conclusion

1. Introduction

Tumor initiation and progression were traditionally described as a consequence of genetic variations; breakthroughs in epigenetic mechanisms provided more evidence to show that epigenetic changes have critical roles in tumor development. Targeting epigenetics appears to be a promising therapy for cancer treatment. Several targeting epigenetic drugs for cancer patients have already obtained approval by the Food and Drug Administration (1).

As epigenetic markers, post-translational modification of histone, involving methylation, acetylation, phosphorylation as well as ubiquitination, SUMOylation, adenosine diphosphate-ribosylation, deimination and proline isomerization, are critical determinants for tumor initiation and progression, which could be passed to daughter cells. A number of previous studies have demonstrated that histone modifications are important for the recruitment or activity of downstream effectors. As aberrant histone modifications are associated with divergent reactions, the present review focuses on histone methylation. Histone methylation was first described in 1964 by Murray (2), and frequently occurs at lysine and arginine residues at the N-terminals of H3 and H4. Histone methylation can engage in either gene activation or silencing depending on specific sites, which may result in the promotion of tumor development (3-5). The lysine residues can be either mono-, di- or tri-methylated, and only the arginine residues can be mono- or di-methylated, and this can have divergent effects on gene transcription (6-9).

As essential tools to ensure accomplished methylation, histone methyltransferases (HMTs) transfer methyl groups from S-adenosyl methionine to the lysine and arginine residues, which further affect gene transcription, chromatin compaction and effector proteins binding (8,10,11). To date, histone methyltransferases has received much attention (Fig. 1), and ~47% of previous studies regarding HMTs were associated with tumor development. Currently, 51 SET domain lysine HMTs, 1 non-SET domain lysine HMT (DOT1L) and 9 arginine HMTs have been identified, and the majority of these are associated with cancer development (11). Misregulation of HMTs shifts the balance of transcription and leads to changes in cell fate, resulting in tumor formation. The following are summaries of the current knowledge of certain histone lysine methyltransferases (HKMTs) and their key sites, whilst exploring the relevance of HMTs and cancer development.
2. Histone lysine methyltransferases

The HKMT family contains an evolutionarily conserved SET domain, which is defined as a 130-amino acid sequence carrying the two most-conserved sequence motifs ELX(FF/YDY) and NHS/CXXPN. It catalyzes the site- and state-specific methylation of different lysine residues with relatively high substrate specificities. There have been 52 family members identified, including 51 SET domain lysine HMTs and 1 non-SET domain lysine HMT, known as DOT1L (12).

Studies have verified that histone lysines 4, 9, 27, 36 and 79 of histone H3 (H3K4, H3K9, H3K27, H3K36 and H3K79), and 20 of histone H4 (H4K20) may be methylated (Fig. 2). Methylation can take three forms: Mono-(-me1), di-(me2) and tri-(me3) methylation. Each histone methylation has a function in regulating transcription and chromatin conformation. H3K4me2/3, H3K9me1, H3K27me1, H3K36me3, H3K79me3 and H4K20me3 are generally enriched in active transcribed regions, while H3K9me2/3, H3K27me2/3 and H4K20me3 are associated with gene repression (13).

H3K9 methyltransferases G9a and SETDB1. Methylation of histone H3K9 is a well-conserved epigenetic marker for transcriptional silencing (14). Histone H3K9 methylation and DNA methylation can work together on the establishment and maintenance of heterochromatin (15). The methyltransferases responsible for histone H3K9 methylation are able to catalyze different substrates and lead to various results (16). These include Clr4/SUV39H1 (17), SUV39H2 (18), G9a (19), GLP/Eu-HMTase1 (20), ESET/SETDB1 (21), Riz1/PRDM2 (22) and CLLD8/KMT1F (23).

Among these HKMTs, G9a is critical for gene silencing and embryonic development. Currently, aberrant regulation of G9a has been identified in a number of cancers (Fig. 3), and is involved in the control of cancer metabolism by maintaining the serine-glycine biosynthetic pathway (24). In PC3 prostate cancer cells, knockdown of G9a significantly inhibits cell growth and induces cellular senescence, and higher G9a expression is associated with poorer prognosis in cancer patients (25). In addition, knockdown of G9a promotes E-cadherin expression in claudin-low breast cancer (CLBC), and inhibited cell migration and invasion in CLBC and lung cancer (26,27). In ovarian cancer, higher G9a expression predicts a greater mortality of patients (28). In neuroblastoma, our previous study reported the importance of G9a in regulating the autophagy signaling pathway, knockdown of G9a inhibited cell growth and proliferation, and the activation of autophagy occurred (29). In acute myeloid squamous cell carcinoma and pancreatic adenocarcinoma, inhibition of G9a induced autophagy-related cell death (30,31). In glioma cancer, previous studies have identified that G9a-dependent H3K9me2 repressed cluster of differentiation 133 and Sox2 expression and in leukemia, and loss of G9a markedly delayed tumor progression and repressed ATRA-mediated leukemia cell differentiation (32,33). Additionally, in head and neck cancer, G9a inhibited stem cell self-renewal (34). G9a was also upregulated in hepatocellular carcinoma (HCC) tissues, and cooperated with the H3K9 methylation effector protein CDYLb, which is involved in HCC development (35,36). In oesophageal squamous cell carcinoma, G9a may serve as an effective prognostic factor and be used as a biomarker (37).

Another key enzyme is SETDB1 (Fig. 3), which has been reported in numerous types of human cancer. SETDB1 was identified in 1999, and the activity of histone H3-K9-specific methyltransferase was reported in 2002 (38,39). SETDB1 is recruited by various transcription factors to regulate gene expression, and is associated with the H3K9me3-enriched genome regions (40). As a constitutive member of promyelo-cytic leukemia-nuclear bodies, SETDB1 has been linked to numerous cellular processes, such as apoptosis, DNA damage responses and transcriptional regulation (41). In melanoma, a study in zebrafish regarded SETDB1 as an oncogene, and indicated its role in regulating tumorigenesis (42). SETDB1 was upregulated in cell lines and tissues in a number of human carcinomas, for example, non-small and small lung cancer, glioma and prostate cancer. In non-small and small lung cancer, recent studies have shown that knockdown of SETDB1 reduced lung cancer cell growth in vitro and in vivo, and overexpression of SETDB1 promoted cancer cell invasiveness (43-46). In glioma, suppression of SETDB1 by siRNA significantly reduced cell proliferation (47). In prostate cancer, downregulation of SETDB1 by siRNA inhibited PCA cell proliferation, migration and invasion (48). Another study reported that a microRNA, known as miR-7, directly targeted SETDB1, and inhibited breast cancer stem cell (CSC) invasion and metastasis, and decreased the breast CSC population, which suggested that SETDB1 activity is important in breast cancer (49).

H3K27 methyltransferase zeste protein-2 (EZH2). Methylation of histone H3K27 is correlated with transcriptional repression (50). Enhancer of EZH2, as a catalytic component of the polycomb repressive complex 2, catalyzes histone H3K27 tri-methylation. To date, >300 studies have reported a close correlation between EZH2 and 46 types of human cancer (Fig. 4). EZH2 is commonly overexpressed in the majority of common cancers, and high EZH2 expression is a prognostic indicator of poor survival. In breast cancer, downregulation of EZH2 blocks the cell cycle, and suppresses cell growth and survival (51-54). In prostate cancer, knockdown of EZH2 inhibits cell proliferation and invasion (55-57). In glioma stem cells, EZH2 is a known target of the MEK-FOXM1 complex, having a critical role in promoting resistance to radiation (58). In glioma and clear cell renal cell carcinoma, downregulation of EZH2 expression can reduce cell proliferation and increase cell apoptosis (59,60). Furthermore, in non-small-cell lung cancer, EZH2 silencing alters the cell cycle by inducing G1/M arrest (61). In lymphoma, overexpression of EZH2 promotes the proliferation and aggressiveness of neoplastic cells, facilitates malignant tumor cell diffusion and mediated transcriptional silencing (62). Additionally, knockdown of EZH2 induces RUNX expression to further inhibit cell proliferation in gastric, breast, prostate, colon and pancreatic cancer cells (63). Furthermore, EZH2 is important in other types of cancer, including malignant peripheral nerve sheath tumor (64), medulloblastoma (65) and lung adenocarcinoma (66).

H3K4 methyltransferase SMYD3. Methylation of H3K4, as an epigenetic phenomenon conserved from yeast to human, is extremely important for transcriptional initiation. It recruits proteins for transactivation, and has reverse functionality to H3K9 methylation. As a common marker of activated genes,
H3K4 tri-methylation provides an epigenetic signature of active enhancers (67). H3K4 methyltransferases include the mixed lineage leukemia (MLL) family (68), SET1A/B (69), absent, small or homeotic disks 1-like (ASH1L) (70), ASH2L (71), SET and MYND domain-containing protein 3 (SMYD3) (72), SET7/9 (73), and SMYD1 (74). However, in mammals, ≥6 H3K4 methyltransferases, including Set1A and Set1B and MLLs 1-4, exhibit histone methyltransferase activity (68). As cardiac- and muscle-specific histone methyltransferases, except for the regulation of early heart development, the oncogenic role of SMYD3 has been identified in different types of cancer. In colorectal cancer, HCC and esophageal squamous cell carcinoma, knockdown of SMYD3 impairs cell proliferation (75,76). Similarly to CRC and HCC, in breast cancer, silencing of SMYD3 also inhibits cell growth, and SMYD3 promotes breast carcinogenesis by directly regulating the protooncogene WNT10B (78). In cervical carcinoma cells and prostate cancer, reduction of SMYD3 expression by doxycycline or small hairpin RNA is able to significantly inhibit cell proliferation, colony formation and migration/invasion activity (79,80).

H3K36 methyltransferases. H3K36 methylation is an indicator of transcriptional elongation, and H3K36 methyltransferases contain nuclear receptor binding SET domain-containing protein 1 (NSD1), NSD2, NSD3 (81), SMYD2 and SETD2 (82). These are involved in diverse biological processes, including small or homeotic disks 1-like (ASH1L) (70), ASH2L (71), SET and MYND domain-containing protein 3 (SMYD3) (72), SET7/9 (73), and SMYD1 (74). However, in mammals, ≥6 H3K4 methyltransferases, including Set1A and Set1B and MLLs 1-4, exhibit histone methyltransferase activity (68).

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alternative splicing and transcriptional repression, as well as DNA repair and recombination (83).

The NSD family is known to be involved in multiple types of cancer, and knockdown of NSD members would suppress cell proliferation and tumor growth. NSD1 specifically mediates methyl transfer onto H3K36 and H4K20. In prostate cancer, NSD1 can enhance androgen receptor transactivation and is associated with prostate tumorigenesis (84,85). In neuroblastoma, overexpression of NSD1 induces tumor suppressor-like features, such as reduced colony formation density and inhibited cell growth (86). NSD1 has been reported in numerous types of cancer, including multiple myeloma (87), acute myeloid leukemia (88,89), lung cancer (90,91) and ganglioglioma (92).

SETD2 is a novel tumor suppressor, which is responsible for H3K36me3 reduction, further resulting in tumor growth inhibition. Mutated SETD2 has been frequently identified in human leukemia, thymic carcinoma (93), renal cell carcinoma (94), non-small cell lung cancer (95) and pediatric glioma (96).

H3K79 methyltransferases. In general, H3K79 methylation correlates with gene transcription (97,98). Disruptor of telomeric silencing 1 (DOT1), the only known H3K79 methyltransferase, participates in the regulation of transcription, development, differentiation and proliferation of normal cells (99). However, the role of DOT1L in cancer cells remains to be elucidated. DOT1L has been shown to interact with multiple MLL fusion partners including AF9, 11-19-leukemia protein, AF10 and AF17. In clinically aggressive acute leukemia, it may be involved in cell survival pathways, and loss of DOT1L activity attenuates cell viability and the colony formation ability (100). However, in lung cancer, downregulation of DOT1L reduces cell proliferation and led to cell cycle arrest at the G1 phase (101).

H4K20 methyltransferases. Methylation of H4K20 has been implicated in multiple biological processes, such as gene transcriptional regulation, cell cycle control, development and genomic integrity maintenance (102,103). Mono- and di-methylated H4K20 have been attributed to DNA replication, DNA damage repair and chromatin compaction. Lack of H4K20me1 results in chromosome condensation in the interphase nucleus. Tri-methylation of H4K20 is required for silencing heterochromatic regions (104).

H4K20 methyltransferases include SUV4-20H1 and SUV4-20H2 (104), PR-Set7/SET8/KMT5A (105), NSD1 (106) and NSD2/WHSC1/MMSET (107). SUV4-20H1 and SUV4-20H2 mediate H4K20me2 and H4K20me3, NSD2 mediates methyl transfer onto H3K4 and H4K20, and PR-Set7 is known as the sole enzyme that catalyzes H4K20me1 (108). In breast cancer cells, overexpression of SUV420H1 and SUV420H2 suppresses cell invasiveness, whereas knockdown of SUV420H2 activates normal mammary epithelial-cell invasion in vitro (109).

3. Conclusion

HMTs have become more important in epigenetics and cancer in recent years. There appear to be numerous connections between SET-domain proteins and cancer. HMTs are important in regulating gene transcription, which may lead to various human malignancies. Among these key sites, H3K9 and H3K27 occupy the majority of the active proteins. Although the functions of HMTs have been explored extensively, the downstream and pathological mechanisms remain to be elucidated.

The present review summarizes the current understanding of HMTs, provides a platform for exploring potential therapy targets through histone modifications, and provides insights into a potential role of aberrant histone modifications in various human malignancies. The aforementioned methylation accumulated the complexity of histone modifications, which provides new insights of these functions in different patterns and their involvement in additional diseases.
Previous studies have provided knowledge about epigenetic heredity, a process whereby genetic information can be preserved through modifications to chromatin without altering DNA nucleotide sequences. Future studies may be able to uncover the molecular mechanisms of histone modifiers, and further studies could perform screening of downstream genes by chromatin immunoprecipitation assays and microarrays to identify the specific target genes and their roles in cancer therapy. This may improve clinical outcomes or predict treatment outcomes for cancer patients.

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