Pathogenic and Therapeutic Role of H3K4 Family of Methylases and Demethylases in Cancers

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Received: 20 March 2019 / Accepted: 26 March 2019 / Published online: 3 April 2019
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Abstract Histone modifications occupy an essential position in the epigenetic landscape of the cell, and their alterations have been linked to cancers. Histone 3 lysine 4 (H3K4) methylation has emerged as a critical epigenetic cue for the regulation of gene transcription through dynamic modulation by several H3K4 methyltransferases (writers) and demethylases (erasers). Any disturbance in the delicate balance of writers and erasers can result in the mis-regulation of H3K4 methylation, which has been demonstrated in several human cancers. Therefore, H3K4 methylation has been recognized as a putative therapeutic or prognostic tool and drug trials of different inhibitors of this process have demonstrated promising results. Henceforth, more detailed knowledge of H3K4 methylation is utmost important for elucidating the complex cellular processes, which might help in improving the disease outcome. The primary focus of this review will be directed on deciphering the role of H3K4 methylation along with its writers/erasers in different cancers.

Keywords H3K4 methylation · Histone methyltransferases · Histone demethylases · Prognosis · Therapeutics · Cancer

Introduction

The term epigenetics belongs to the changes in gene expression without altering the underlying DNA sequence [1, 2]. The epigenetic mechanism mainly includes DNA methylation, nucleosome remodeling, non-coding RNAs, and post-translational histone modifications, which controls the expression of genes by hindering the access of various transcription factors for DNA. In contrast to genetic aberrations, epigenetic phenomena are biochemically reversible, making them exciting tools to study in the context of cancer biology [3]. Histones are not merely packaging material for DNA as thought earlier, but regarded as the distinct molecular entities, regulating gene expression. Each core histone consists of a histone fold and two unstructured histone tails. These unstructured N- and C-terminal tails project outside the DNA gyres and are densely post-translationally modified by number of modifications like acetylation, methylation, sumoylation, ubiquitylation, phosphorylation, ADP ribosylation, deimination, biotinylation, butyrylation, N-formylation, and proline isomerization [4, 5]. These histone post-translational modifications (PTMs) are dynamic and maintained by two classes of enzymes known as writers and erasers of histone modifications and read by a special group of enzymes called readers of histone modifications. The combination of all types of histone modifications constitutes a ‘histone code’ of the cell [6]. This review will specifically focus on histone 3 lysine 4 (H3K4) methylation and its role in cancer biology in the context of prognostic or therapeutic targets.

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Histone Methylation

Among all histone modifications, methylation has appeared to be a key epigenetic signature in regulating gene expression. Histone methylation mostly occurs on lysine and arginine residue on histone tail but can also involve other amino acids such as aspartic acid, histidine and glutamic acid and carboxyl group of different proteins. Among 24 positions of histone methylation discovered till now, 17 are lysine and 7 are arginine residues [7]. The arginine residue can be mono- or di-methylated, the later in symmetrical or asymmetrical form. In contrast, lysine can be mono-, di- or tri-methylated [8, 9]. However, unlike acetylation, no alteration in the net charge of the histone protein occurs during methylation. Rather, methylation brings about the transcriptional change by recruiting various effector proteins, known as histone methylation readers. It can thus result in either activation or suppression of a gene, based on the site of the group to be methylated along with number of methyl groups attached [7]. Generally, histone 3 lysine 4 methylation (H3K4me), histone 3 lysine 36 methylation (H3K36me) and histone 3 lysine 79 methylation (H3K79me), result in gene activation, while histone 3 lysine 9 methylation (H3K9me), histone 3 lysine 27 methylation (H3K27me) and histone 4 lysine 20 methylation (H4K20me), result in gene repression [10, 11]. Apart from histones, lysine methylation can also takes place on several non-histone proteins particularly, transcriptional and chromatin-regulating proteins that further complicate the histone code [12]. Methylated histones are sensed and linked to downstream biological functions by an array of methyl lysine-binding proteins, which contains chromo-domains or plant homeodomains (PHDs) [13]. Thus, numerous positions and arrangements of methylation generate tens of thousands of patterns of methylated histones, increasing both the complexity and diversity of histone methylation code. Therefore, lysine methylation seems to play an essential role in many downstream cellular processes, such as replication, DNA damage response, cytokinesis, cell cycle and transcriptional regulation of important developmental and tumor-suppressor genes [4]. Histone methylation of lysine residues is maintained by specific classes of enzymes known as lysine methyltransferases (KMTs) and lysine demethylases (KDMs) [14].

H3K4 Methylation

Generally recognized as a mark of gene activation, H3K4me3 selectively localizes at promoter region of gene along with transcriptional start sites and thereby, regulates gene transcription; on the other hand, H3K4me1 and

H3K4me2 are linked with enhancer elements and transcriptionally active genes. [11]. The methylation of H3K4 is performed by SET [Su (var), Enhancer of Zeste, and Trithorax] domain-containing enzymes, which are in turn, part of bigger protein complexes that can catalyze all the three methylation marks of H3K4 i.e., mono- di- and tri-methylation [15]. The founding gene of the MLL/Set1 protein family, Set1, forms a multiprotein unit known as COMPASS (COMplex of Proteins ASSociated with Set1) in *Saccharomyces cerevisiae*. Set1/COMPASS was the initial H3K4 methyltransferase identified in yeast. It is capable of carrying out mono-, di-, and trimethylation of H3K4 [16]. In contrast, *Drosophila* contains three different Set1-like H3K4 methyltransferase complexes containing unique enzymatic subunits, which are accountable for their H3K4 methyltransferase activity. These are dSet1, Trithorax (Trx), and Trithorax-related (Trr). While, dSet1 is involved in carrying out the bulk of H3K4me3, Trr was known to regulate H3K4me1. On the contrary, mammals have six different Set1-like H3K4 methyltransferases: KMT2A (MLL1), KMT2B (MLL2), KMT2C (MLL3), KMT2D (MLL4), KMT2F (SET1A), and KMT2G (SET1B) [17]. Other than Set1 family, SMYD and NSD families are also known to write H3K4 methylation code [18].

For many years, histone methylation baffled the scientists, as histone degradation was the only way of reversing the histone methylation effect. However, in 2004 the discovery of histone lysine-specific demethylase 1 (LSD1), also called as BHC110, AOF2, or KDM1, which is capable of demethylating H3K4me1 and H3K4me2, paved the path for future research [19]. The discovery of LSD1 has transformed the whole idea of histone methylation as a dynamically coordinated process, which is under enzymatic control, rather than histone marks which could only be changed by replacement or ubiquitylation of histone. After that, plethora of histone methyltransferases and demethylases have been discovered that regulate the addition and removal of particular methyl groups from various lysine residues on histone proteins [18, 20]. Generally, there are two categories of histone demethylases: FAD-dependent monoamine oxidases (MAO) and jumonji C (JmjC)-domain-containing, iron-dependent dioxygenases that catalyze the demethylation of histones and non-histone substrates [21, 22]. While LSD1 possesses specificity only toward mono- and di-methylated H3K4, the JmjC domain demethylases can act on tri-methylation also. There exist about 30 JmjC domain-containing proteins, each of which has unique histone residue-specific demethylating capabilities [23]. FBXL11 (JHDM1a or KDM2A) was the first JmjC domain containing demethylase, which can specifically act on mono- and dimethylated H3K36 [24] (Fig. 1).

Table 1 Histone modifications (H3K4me) in the prognosis of human cancers

Associated cancer	Histone modifications	Alteration in cancer	Outcome	References
Renal cancer	H3K4me1/2/3	Decreased	Poor prognosis	[28, 34]
Non-small cell lung carcinoma	H3K4me2	Increased	Greater survival	[29]
Pancreatic ductal adenocarcinoma	H3K4me2	Decreased	Poor survival	[31]
Prostate cancer	H3K4me1	Increased	Higher recurrence	[32, 33]
	H3K4me2	Increased	Higher recurrence	
Breast cancer	H3K4me2	Decreased	Poor prognosis	[30]
Colorectal cancer	H3K4me2	Increased	Worse prognosis	[91–93]
	H3K4me2	Decreased	Poor survival	
	H3K4me3	Decreased	Good prognosis	
Bladder cancer	H3K4me1	Decreased	Poor prognosis	[94]
Hepatocellular carcinoma	H3K4me3	Increased	Poor prognosis	[35]

leukemogenesis can also occur as a consequence of loss-of-function mutations of MLL [38]. Apart from MLL1, four other members of this HMT family, MLL2–MLL5 were also found to be mutated and amplified in human cancers [39, 40]. Ash2L mRNA levels are not altered or mutated in human cancers, but protein levels were found to be frequently increased in different tumor cells as compared to the corresponding normal cells in larynx and melanoma, squamous cell carcinomas of cervix, rhabdomyosarcoma, adenocarcinoma of the pancreas, and colon and breast cancers [22]. The over-expression of KMT2F gene was associated with breast, colorectal and bladder cancers [41, 42]. Our group showed the overexpression of KMT2G in higher stages of RCC as well as with metastasis of the tumor [43].

In KMT3 family of H3K4 methyltransferases, NSD2 expression was reported to promote clonogenic growth, cell-to-cell adhesion, and tumorigenicity in multiple myeloma and expression correlating with tumor proliferation activity in glioblastoma multiforms [44]. NSD2 was linked with tumor aggressiveness or prognosis in different types of cancers [45]. NSD3 was identified to be amplified in breast cancer cell lines and also in primary breast carcinomas [46]. Over-expression and amplification of NSD3 was also reported in several pancreatic ductal adenocarcinoma [47, 48].

SMYD1, expression of which is limited to muscle tissues only, was found to be over-expressed in rhabdomyosarcoma [49]. Another H3K4 HMT, i.e. SMYD3 is recognized as an oncogenic activator as its up-regulation in HCC, and colorectal carcinoma resulted in increased H3K4 methylation and reactivated normally silent oncogenes [50]. SMYD3 levels were also demonstrated to be higher in most breast cancer tissues, and elevated SMYD3 levels are important for the proliferation of breast cancer cells. Also, SMYD3 contributes to breast carcinogenesis by directly

controlling the expression of the proto-oncogene, Wnt [51]. Also, knockdown of SMYD3 expression using small interfering RNAs (siRNAs) inhibited cell cycle progression in cancer cell lines, making it a putative drug target for anti-cancer therapy [50]. SMYD2, which is another HMT for H3K4 position, has been found to be overexpressed in various cancers including esophageal squamous cell carcinoma. A study by Reynoird et al. demonstrated the growth-enhancing role of SMYD2 in pancreatic cancer and pharmacological inhibition of SMYD2 restricts pancreatic ductal adenocarcinoma growth. [52, 53]. Promoter DNA hypermethylation of the SMYD3 gene was also associated with higher risk of colorectal cancer [54]. Additionally, SMYD3 and SMYD2 are known to harbor prognostic significance in both univariate and multivariate models for cancers. SMYD3 act as a prognostic parameter in HCC and PCa [55, 56]. Similarly, SMYD2 was found to have independent prognostic value for patients with primary HCC and papillary thyroid carcinoma [57, 58]. The deregulation of various H3K4 methyltransferases in cancers is summarized in Table 2.

Aberrant Expression of Various H3K4 Demethylases in Human Cancers

LSD1, which is the first histone demethylase to be discovered, was principally existing as H3K4 demethylase but it is believed by some scientists to be capable of altering its substrate specificity toward H3K9 demethylation in the presence of androgen receptor (AR). Henceforth, LSD1 was shown to a component of both repressive and activating complexes [59]. But, the enzymatic activity and specificity of LSD1 has to be identified by its associated partners, which includes CoREST and AR. When binds with the repressive CoREST complex, it plays a role

Table 2 Involvement of various H3K4 methyltransferases in cancer

H3K4 HMTs	Alteration	Associated cancer	References
MLL1	Translocation, amplification, tandem duplication	Human lymphoid and myeloid leukemia's, myelodysplastic syndrome, head and neck cancer	[36, 95, 96]
MLL2	Recurrent mutations	Esophageal sarcomatoid carcinoma, prostate cancer, Gastric cancer	[40, 97, 98]
MLL3	Mutations and under-expression	Lung adenocarcinoma, bladder, breast cancers, gastric adenocarcinoma	[99–102]
MLL4	Mutations, downregulation, over-expressed	Lymphoma, medulloblastoma, gastric cancer, pancreatic cancer	[103–105]
MLL5	Overexpressed, mutations, under-expression	AML, gastric cancer, colorectal cancer, breast cancer	[106–108]
hSET1A	Overexpressed	Bladder cancer, breast cancer, colorectal cancer	[41, 42]
hSET1B	Mutations, overexpressed	Gastric cancer, colorectal cancer, and RCC	[43, 109]
ASH2L	Overexpressed	Breast cancer, rhabdomyosarcoma, colon cancer	[22, 110]
SMYD1	Mutations, overexpressed	Splenic marginal zone lymphoma, rhabdomyosarcoma	[49, 111]
SMYD2	Overexpressed	Esophageal squamous cell carcinoma, HCC, breast cancer, papillary thyroid carcinoma	[52, 57, 58, 112]
SMYD3	Overexpressed	Colon cancer, HCC, prostate cancer	[50, 55, 56]
NSD2	Overexpressed, mutations	Lung cancer, osteosarcoma, acute lymphocytic leukemia	[45, 113, 114]
NSD3	Amplification, overexpressed	Pancreatic ductal adenocarcinoma, NSCLC, bladder, breast, liver, lung cancers	[47, 48, 115]

of H3K4me2/me1 demethylase, while in a complex with AR, it serves as a transcriptional activator, demethylating H3K9me2/me1 [59, 60]. LSD1 has also been shown to be associated with estrogen receptor (ER) signaling [61]. Studies using ELISA method showed that LSD1 was highly augmented in ER-negative breast tumors and there it might act as a potential marker for aggressive breast tumor and thereby, a novel attractive drug target for treatment of ER-negative breast cancers [62]. LSD1 overexpression was also found in HEK 293 cells, which leads to a decrease in H3K4 methylation, thereby silencing transcription [63]. LSD1 overexpression has also been reported in PCa, where it was reported to be a predictive biomarker for prostate cancer [64]. Recently, it was demonstrated that LSD1 interacts with transcriptional factor GFI1 that in turn leads to tumorigenesis in medulloblastoma [65]. Nagasaka et al. [66] showed that LSD1 is a direct target of c-Myc delineating the other interaction of LSD1 with transcription factors, and LSD1 mRNA levels were associated with c-Myc expression in human acute myeloid leukemia (AML), gastric adenocarcinoma, glioblastoma, and prostate adenocarcinoma.

On the contrary to LSD1, the studies on LSD2 are limited. LSD2 was elevated in pancreatic cancer tissues and pancreatic cancer cell lines (BxPC-3, CFPAC-1, PANC-1 and SW1990) and reported to be involved in the cell proliferation and apoptosis [67]. In another study by Katz et al. [68] LSD2 was demonstrated to be highly expressed in breast cancer and participate in gene silencing

by regulating DNA methylation. Cao et al. [69] also showed the relationship between LSD2 and DNA methyltransferases in small cell lung carcinoma, indicating the importance of combined epigenetic therapy in the treatment of cancer.

Although FBXL10 is primarily H3K36 demethylase, it also shows activity against H3K4 position [13]. FBXL10 was found to be over-expressed in pancreatic ductal adenocarcinoma, and its expression was correlated with the stage, grade, and metastasis of the tumor [70]. FBXL10 was also shown to induce cell proliferation and autophagy in gastric cancer [71].

Among JmjC family, which consists of four members: JARID1A, JARID1B, JARID1C, and JARID1D (KDM5A-D) capable of demethylating tri- and di- methylated H3K4, the KDM5A overexpression was found in gastric cancer and its inhibition promoted cellular senescence of gastric and cervical cancer cells through derepression of cyclin-dependent kinase inhibitors, like p27, p21 and p16 [72]. The role of H3K4 demethylases was also implicated in drug resistance in cancer cells. For example, the expression of KDM5A was increased in drug-tolerant PC9, a prostate carcinoma cell line. Also, the knockdown of KDM5A decreased the number of drug-tolerant cells and contrarily, higher expression of KDM5A in PC9 cells reduced the sensitivity for the whole population [73]. Additionally, KDM5A was correlated with poor prognosis in RCC and increased the cancer stem-like phenotype in RCC cells [74]. The overexpression of KDM5B has been

reported in breast and PCa and involved in proliferation of MCF-7 cells by enhancing G1 progression [75, 76]. Also, inhibition of KDM5B resulted in significant decrease of MCF-7 cell proliferation and augmented the expression of specific tumor suppressor genes, including, BRCA1, CAV1, and HOXA5 [77]. KDM5B over-expression was correlated with poorer survival in NSCLC and HCC where it act as a prognostic indicator [78, 79]. KDM5B also lead to chemoresistance in some cancer cells as inhibition of KDM5B led to re-sensitization towards paclitaxel in endometrial carcinoma. [80] Another Jumonji domain containing H3K4 demethylase KDM5C was found to be over-expressed in acute monoblastic leukemia [81]. Like the other two members of the family, KDM5C is also involved in drug resistance in colon cancer cell lines [82]. In addition, somatic mutations of KDM5C have been identified in different cancers, actively supporting the role of these enzymes in tumorigenesis. According to several studies, KDM5C gene has been treated like a tumor suppressor [83, 84]. On the contrary to the other three members, loss of KDM5D expression is linked to docetaxel resistance in prostate cancer due to a disturbance in the interaction of KDM5D with AR [85]. Low expression of KDM5D was also related to poor prognosis in prostate cancer patient's [86]. All these studies indicated the tumor suppressive role for KDM5D in cancer. The alterations of HDMs in cancers are classified in Table 3.

Therapeutic Potential of H3K4 Modifiers

Epigenetic alterations are reversible in nature, which makes them an attractive drug target for cancer treatment. The alteration or imbalance in the function of histone

modifiers is involved in the malignant growth, and thus, the development of novel therapies directed against these enzymes might be beneficial for cancer treatment. Most of the success has been achieved in case of histone deacetylase inhibitors (HDACi) for treating hematological malignancies, for example, Vorinostat and Romidepsin are the FDA approved HDACi for the treatment of cutaneous T cell lymphoma [87]. Besides histone acetylation, inhibitors of histone methylation and demethylation are mostly in clinical or pre-clinical trials. LSD1 shows similarities in its active site to the flavin-dependent MAO that also involves in removing the amine groups in an oxidative manner. MAO inhibitors were looked for their capacities to inhibit LSD1 and as a result, tranylcypromine, and phenelzine were reported to inhibit LSD1 activity with the highest potency (IC₅₀ = 21 μM) [23]. GSK2879552 and ORY-1001 (tranylcypromine derivatives) are specific inhibitors for LSD1 and are currently going through drug trials for small cell lung carcinoma and relapsed or refractory AML, respectively [88]. In contrast to individual therapy, combination of epigenetic therapy with chemotherapy was shown to be more effective. A pre-clinical study in a xenograft model of glioblastoma showed that a combination of vorinostat and tranylcypromine (KDM1A inhibitor) could inhibit tumor cell growth [89]. In context to HMT inhibitors, Novobiocin, which is HSP90 inhibitor, was also shown to reduce the expression of SMYD3 thereby suppressing the proliferation of human breast cancer cells [90]. Currently, epigenetic therapies are successful in the treatment of hematological malignancies as indicated by clinical studies, but little success has been achieved in the case of solid tumors. Therefore, detailed knowledge of the roles of the epigenetic regulators such as writers, readers, and erasers in human cancers may offer a

Table 3 Association of H3K4 demethylases with different cancers

H3K4 HDM	Alteration	Associated cancer	References
LSD1	Overexpressed	Prostate cancer, AML, breast cancer	[62, 64, 66, 116]
	Low expression	HCC	
LSD2	Overexpressed	Pancreatic cancer, breast cancer, lung cancer	[67–69]
FBXL10	Mutations, Low expression; Overexpressed	Lymphoma, brain, glioblastoma multiforme, pancreatic ductal adenocarcinoma, gastric cancer	[70, 71, 117]
JARID1A	Overexpressed	Gastric cancer, prostate cancer, breast cancer; esophageal sarcomatoid carcinoma	[72, 73, 98, 118]
	Mutation		
JARID1B	Overexpressed	Breast cancer, prostate cancer, NSCLC, HCC	[75, 76, 78, 79]
JARID1C	Inactivating mutations	Clear cell RCC	[81, 83, 84]
	Overexpressed	Acute monoblastic leukemia	
JARID1D	Deletions	Prostate cancer	[86, 119]
	Low expression		

new therapeutic approach for treating different malignant conditions.

Conclusion

During the last decade, much progress has been made in the area of histone modifications and in deciphering their role in human cancer. But decoding the role of histone modifications in cancer pathogenesis is a daunting task due to the complex and highly dynamic nature of the post-translational modifications. H3K4 methylation is generally associated with active transcription and showed occupancy at promoter and enhancer regions of the gene. Global deregulation of H3K4 modification along with their modifiers play a vital role in the development and progression of various cancers. Various studies reported the use of H3K4 methylation as an independent prognostic indicator for different cancers, but this is still in its infancy stages mainly because of lack of specificity and cross-talk with other histone modifications. Since histone modifications are reversible, restoring to their original state by epigenetic targeting strategies will be very promising and therapeutically relevant. Although despite advancement in the targeting of histone modification for cancer therapeutics, only HDACs inhibitors are currently approved by the FDA for hematological malignancy. Most of the histone methyltransferases and histone demethylases inhibitors are still in the preclinical stages. Henceforth, it is here desirable to develop additional drugs targeting other histone modifiers and to use them in the combination therapy, which can improve the outcome of the disease. The molecular mechanisms associated with each histone modifier are still needed to be elucidated so that more therapeutic options can be made available in the future.

Author's Contribution All authors are involved in the design, preparation of manuscript, read and final approval of the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest.

Ethical Approval This is a review article and does not involve experiments with human subjects or animals performed by any of the authors.

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