Histone Modification and Cancer

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The nucleosome is the basic unit of chromatin. It is an octamer composed of 4 core histones (H3, H4, H2A, H2B), including one H3-H4 tetramer and two H2A-H2B dimers, surrounded by 147 pairs of DNA base pairs. The core histones form a spherical core particle, and their N-terminal tails are free from the core particle, which helps the modification occur. Posttranslational modifications (PTMs) are involved in a variety of cellular processes, such as transcription, DNA damage, apoptosis, and cell cycle regulation. Mass spectrometry is a powerful tool for finding and verifying histone PTMs.

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1. Histone Methylation in Cancer

Histone methylation, including monomethylation, demethylation, and trimethylation, is regulated by methyltransferases and demethylases and occurs mainly on lysine residues of H3 and H4 [1]. H3K4me1/2/3, H3K36me1/2/3, and H3K79me1/2/3 are transcriptionally active marks, while H3K9me1/2/3 and H3K27me3 are transcriptionally repressive marks [2]. Histone methylation disorder leads to the destruction of gene expression and genomic stability, and the abnormal modification of histone methylation in tumor cells can alter cancer development (**Table 1**). For example, decreased H3K27me3 and increased H3K4me3 activate the Wnt/β-catenin signaling pathway to promote colorectal cancer cell development [3]. Mutations in histone methylation sites (H3K27M, H3K27I, etc.) are present in approximately 30% of children with glioblastoma [4]. NSD2 maintains genome integrity and reduces disease incidence by methylating H3K36 and DOT1-mediated H3K79 methylation in response to UV radiation-induced DDR [5]. Under normal physiological conditions, the number of H3K9me3 increases dramatically over time at the site of DNA double-strand break damage and participates in DDR. In contrast, in the environment of abnormal tumor cell metabolism, abnormal H3K9me3 inhibits DNA repair [6].

Histone methylation has been used as a promising target for cancer therapy. A large number of methyltransferase inhibitors have been developed and entered clinical trials, mainly against H3K27 and H3K79 methyltransferase, and arginine methyltransferase [7]. EZH2, a methyltransferase of H3K27, is involved in tumor occurrence, metabolism, drug resistance, and immune regulation [8]. Therefore, targeting EZH2 for cancer therapy has become a hot research topic. Strategies for EZH2 inhibitors include targeting methyltransferase activity (GSK126, GSK343, EPZ011989, et al.), breaking PRC2's structure (SAH-EZH2, Astemizole, MAK683, et al.), or triggering EZH2 degradation (GNA022, ANCR, FBW7, et al.) [8]. For example, EZH2 inhibitor GSK343 can decrease self-renewal and increase sensitivity to chemotherapy in colorectal cancer cells [9]. Some studies have also shown that EZH2 has an antitumor effect [10][11]. For example, GSK126 can increase the number of myeloid-derived suppressor cells

(MDSC) and decrease the number of $IFNy^{+}CD8^{+}$ T cells, leading to the failure of antitumor therapy. Interestingly, when combined with neutralizing antibodies against the myeloid differentiation antigen GR-1, MDSC-mediated immunosuppression was mitigated and increased the therapeutic effect of GSK126 [12]. Developing a multi-drug combination therapy strategy may address the limitations of single drug therapy. These studies indicate that histone methylation modification plays an important role in the development and prevention of cancer.

Table 1. The role of genes encoding histone methyltransferase in human cancer.

Gene	Tumor	Role	Reference
SETD1A	Colorectal cancer, Lung cancer, Gastric cancer	Oncogenic	[13][14][15]
SETD1B	Pancancer	Suppressor	[16]
MLL1	Breast cancer, Cervical carcinoma, Acute myeloid leukemia	Oncogenic	[17][18][19]
MLL2	Bland cancer, Prostate cancer	Suppressor	[20][21]
MLL3	Nasopharyngeal carcinoma, Breast cancer, Pancreatic cancer, Colorectal cancer	Ambiguous	[22][23][24][25]
MLL4	Lung cancer, Medulloblastoma,	Suppressor	[26][27]
SMYD2	Lung cancer, Cervical cancer	Oncogene	[28][29]
SET7	Glioma, Colorectal cancer, Lung cancer	Suppressor	[30][31][32]
SET9	Glioma, Lung cancer, Breast cancer	Suppressor	[30][32][33]
SMYD3	Pancreatic cancer, Lung cancer, Breast cancer	Overexpression	[34][35][36]
SUV39H1	Cervical cancer, Prostate cancer, Melanoma	Oncogene	[37][38][39]
SUV39H2	Colorectal cancer, Osteosarcoma, Lung cancer	Oncogene	[40][41][42]
G9A	Colorectal cancer, Bladder cancer, Lung cancer, Breast cancer	Oncogene	[43][44][45][46]
SETDB1	Lung cancer, Gastric cancer, Colorectal cancer	Oncogenic	[47][48][49]
PRDM3	Pancreatic ductal adenocarcinoma	Suppressor	[50]
PRDM16	Kidney cancer, Prostrate cancer, Lung cancer	Suppressor	[51][52][53]
EZH1	Breast cancer, Hepatocellular carcinoma	Oncogenic	[54][55]
EZH2	Lung cancer, Hepatocellular carcinoma, Breast cancer, Gastric cancer, Colorectal cancer	Oncogene	[55][56][57][58][59]
SETD2	Prostate cancer, Pancreatic cancer, Leukemogenesis,	Suppressor	[60][61][62][63]

Gene	Tumor	Role	Reference
	Hepatocellular carcinoma		
NSD1	Pancreatic cancer, Laryngeal cancer	Oncogenic	[64][65]
NSD2	Lung cancer, Colorectal cancer, Breast cancer, Renal cancer, Osteosarcoma, Prostate cancer	Oncogene	[66][67][68][69][70][71]
NSD3	Lung cancer, Breast cancer, Colorectal cancer, Pancreatic cancer	Oncogene	[72][73][74]
SETD3	Breast cancer, Hepatocellular carcinoma	Overexpression	[75][76]
ASH1L	Prostate cancer, Leukemia	Oncogenic	[77][78]
SETMAR	Acute myeloid leukemia	Suppressor	[79]
PRDM9	Pancancer	Overexpression	[80]
DOT1L	Prostate cancer, Colorectal cancer, Gastric cancer, Ovarian cancer, Breast cancer, Acute myeloid leukemia	Overexpression	[18][81][82][83][84][85]
SET8	Prostate cancer, Hepatocellular carcinoma, Breast cancer	Oncogenic	[86][87][88]
SUV4-20H2	Hepatocellular carcinoma, Breast cancer	Suppressor	[89][90]

ses (HAT)
ation and
shutdown of gene transcription. HATs transfer the acetyl group from acetyl-CoA to the amino terminal of the specific lysine residue of the histone, generating an acetate bond. Acetylation is a key epigenetic mechanism in gene regulation [91] and regulates chromatin structure and function through transcriptional capacity [92][93]. Abnormal histone acetylation can disrupt cell homeostasis and affect cell metabolism and gene regulation [94]. Cumulative evidence suggests that abnormal expression of histone modification enzymes is closely related to tumor development (**Table 2**). The current antitumor treatment of histone acetylation as a therapeutic target is expected to be achieved through the development of HAT and HDAC inhibitors. The first HDAC inhibitor approved for clinical treatment was suberoylanilide hydroxamic acid (SAHA), and more drugs are being developed, such as YF479, which has good antitumor activity and can inhibit the recurrence and metastasis of breast cancer [95][96]. Thus, histone acetylation modification plays a significant role in the occurrence and development of cancer.

Table 2. The role of genes encoding histone acetyltransferase in human cancer.

Gene	Tumor	Role	Reference
HAT1	Liver cancer, Pancreatic cancer, Cholangiocarcinoma	Overexpression	[97]
GCN5	Colorectal cancer	Overexpression	[98]
PCAF	Lung cancer, Esophageal cancer	Ambiguous	[99][100]
Tip60	Prostate cancer, Breast cancer	Ambiguous	[101][102]
MOF	Bladder cancer, Endometrial cancer, Renal cell carcinoma	Suppressor	[103][104][105]

Gene	Tumor	Role	Reference
MOZ	Gastrointestinal stromal tumor, Acute myeloid leukemia	Oncogene	[106][107]
MORF	lymphoma	Oncogene	[108]
HBO1	Lung cancer, Osteosarcoma, Hepatocellular carcinoma, Breast cancer	Oncogenic	[109][110][111][112]
p300	Esophageal cancer, Prostate cancer, Lung cancer	Oncogenic	[100][113][114]
CBP	Colorectal cancer	Oncogenic	[82]

Ubiquitin (Ub) exists widely in eukaryotes, and ubiquitination is also one of the main posttranscriptional modifications. Posttranslational modification of proteins is a reversible, dynamic process. Histone ubiquitination is dynamically regulated by ubiquitination enzymes and deubiquitination enzymes and can participate in most intracellular processes, including protein degradation, intracellular signaling, endocytosis, and DNA damage reactions [115][116][117]. Histone ubiquitination is the core event of DDR, and DNA damage requires a large number of ubiquitin molecules, which are crucial for preventing abnormal DNA repair and maintaining genomic stability [118]. Histone H3 ubiquitination enzymes mainly include NEDD4 and CUL4A. NEDD4 ubiquitinates histone H3 on lysine 23/36/37 residues in a glucose-dependent manner, specifically recruiting the histone acetyltransferase GCN5 for subsequent H3 acetylation. This mechanism can regulate gene transcription and tumorigenesis in cancer [119]. The RNA demethylase ALKBH5 and the USP22/RNF40 axis regulate histone H2AK119 monoubiquitination to regulate the expression of key genes involved in DNA repair, thus playing a crucial role in the development of osteosarcoma [120]. Rad6 and Bre1 form a well-characterized H2B monoubiquitin enzyme to degrade histones in DDR reactions [121]. USP11 can deubiquitinate H2AK119 and H2BK120 to separate ubiquitin molecules from histones and maintain genomic stability [122]. It is worth noting that the existing studies on histone ubiquitination mainly focus on histone H2A/H2B, and the discovery of histone H3 ubiquitination and the study of its mechanism are also gradually deepening. However, the regulation of histone H3 deubiquitination remains unclear.

4. Histone Phosphorylation in Cancer

Histone phosphorylation occurs on serine and tyrosine residues of histones and has been shown to be involved in many cellular life activities, including DNA damage repair, gene transcription, chromatin maintenance and aging, through histone methylation [123][124]. For example, PRK-mediated H3T11 phosphorylation (H3T11ph) hastens the removal of repressive histone H3 lysine 9 (H3K9) methylation by JMJD2C, demonstrating a unique mechanism by which histone phosphorylation activates gene expression. Importantly, the level of H3T11ph correlates with prostate cancer malignancy, suggesting that inhibition of H3T11ph may be a promising therapeutic target [125]. Phosphorylated H3.3 (H3.3S31ph) enhances the binding of the methyltransferase SETD2 to histone proteins, thus promoting gene transcription and highlighting the causal role of H3.3 phosphorylation in tumor metastasis [126]. H3.3S31ph is also involved in the regulation of heterochromatin regions and reduces the demethylation of H3K9me3 to maintain chromatin integrity by downregulating the activity of KDM4B [127]. Pyk1-catalyzed H3T11ph can weaken the binding of Dot1 to chromatin and reduce Dot1-mediated H3K79me3, leading to suppression of autophagy-related gene transcription and uncovering histone modification crosstalk in response to cell metabolism

[128]. Additionally, a recent study showed that phosphorylation of histone H3 at serine 10 inhibits methylation of histone H3 at adjacent arginine 8, providing a framework for understanding the effects of phosphoserine on the methylation of adjacent amino acid residues and arginine [129]. In order to function, histone phosphorylation may antagonize its methylation.

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