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Roles of Histone Modifications in Gastrointestinal Tumorigenesis

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Abstract

Histone modifications play important roles in gastrointestinal tumorigenesis as tumor suppressors or oncogenic drivers depending on the type of tumor and histone modification. The diversity of histone modifications leads to a remarkable complexity in the functions and mechanisms they regulate, which are gradually beginning to be elucidated. This review concentrates on current research regarding the roles of histone modifications and associated histone-modifying enzymes in gastrointestinal tumorigenesis.

Keywords: Histone modification; Tumorigenesis; Epigenetics

Impact Statement

Epigenetics is a branch of genetics, and the connection between histone modifications and tumorigenesis has been a promising field for cancer research. The diversity of histone modifications leads to a remarkable complexity in the functions and mechanisms that are gradually beginning to be elucidated. The dynamic balance of histone modifications and their effects are crucial for gastrointestinal tumorigenesis. Histone-modifying enzymes have been the targets of therapeutic agents. These enzymes have either been authorized for cancer treatment or are under development in clinical trials.

Introduction

The term "epigenetics" was originally used to describe the mechanism of heritable changes in a cellular phenotype that were related to the control and modification of expression of genetic materials without any changes in DNA sequences [1]. Epigenetic changes are reversible and may lead to loss or gain of certain biological functions. The three most well-known mechanisms of epigenetic regulations of gene expression involve changes in: (i) DNA methylation; (ii) histone modification; and (iii) RNA-associated silencing.

Eukaryotic DNA has a complex three-dimensional structure and is condensed within the cell nucleus by means of associations with histones. These DNA-histone complexes are the primary components of chromatin in eukaryotic cells. The chromatin forms a "beads-on-a-string" structure, and its basic unit is the nucleosome, which is highly conserved in various species and repetitive throughout the whole genome. The nucleosome is composed of a histone core that is wrapped around by two loops of DNAs (approximately 147 bp). A histone linker H1, which binds nucleosomes, is involved in condensation of chromatin [2]. The histone core is an octamer consisting of pairs of each of the four core histone proteins (H2A, H2B, H3, H4) [3,4]. Altered or abnormal chromatin conformation has also now been recognized as an epigenetic hallmark of many cancers.

Histone modifications can affect the interactions between histone proteins and DNAs as well as between adjacent histone proteins. Histone modification is critical for the regulation of normal cellular functions, while dysfunction of histone modification attributed to aberrant expression, mutation, or translocation, results in pathological conditions, such as gastrointestinal cancer. Over recent decades, the connection between epigenetics and gastrointestinal tumorigenesis has become a promising field for cancer research [5].

It is well known that histone-modifying enzymes participate in gastrointestinal tumorigenesis, acting as oncogenic drivers or tumor suppressors depending on the specific histone-modifying enzymes or types of cancer. In this review, we focus on the current knowledge regarding the roles of histone modifications and associated histone-modifying enzymes in gastrointestinal tumorigenesis.

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Histone Modifications and Gastrointestinal Tumorigenesis

Since Allfrey et al. [6] proposed the concept that histone modifications have a functional influence on the regulation of transcription in 1964; researchers have learned that these modifications have a major influence not only on transcription but also in numerous chromatin-related processes, such as gene transcription, DNA repair, DNA replication, DNA recombination, and chromosome segregation [7]. The diversity of histone modifications leads to a remarkable complexity in the functions and mechanisms they regulate and which are gradually beginning to be elucidated. Using transcription as an example, we know that multiple co-existing histone modifications are associated with transcription activation, while others are associated with repression. The state of histone modifications is dynamically balanced by two enzyme families with converse catalytic activities: Histone-modifying and de-modifying enzymes.

There are several types of histone modifications, including phosphorylation, ubiquitination, acetylation, methylation, SUMOylation, Biotinylation, citrullination, poly-ADP ribosylation, N-glycosylation, and proline cis-trans isomerization. A summary of histone modifications and associated histone-modifying enzymes in tumorigenesis is provided in Figure 1. They are shown to directly or indirectly influence chromatin structures and in turn tumorigenesis. Meanwhile, numerous histone-modifying enzymes have been identified and characterized by performing post-translational covalent modifications by attaching different portions to specific residues on the tails of histones. Moreover, the dysregulation of these modifications can lead to abnormal gene expression related to tumorigenesis, relying on the modification pattern of the amino acid residues on histone tails.

Gastrointestinal tumors, mainly including gastric and colorectal tumors, account for a large proportion of human malignancies. Gastric cancer is the fourth most frequently occurring cancer worldwide, and originates from the mucosal epithelial cells located in the superficial layer of the gastric wall. It can therefore occur in various regions of the stomach. Colorectal cancer is the third most common cancer in humans, with five-year survival rates of only less than 15% when tumors spread to distant sites. Major advances in molecular and cellular technologies over the past 20 years have led to a better understanding of the mechanisms of gastrointestinal tumorigenesis. Moreover, it has been well reported in recent years that histone modifications and associated histone-modifying enzymes play important roles in gastrointestinal tumorigenesis.

Histone phosphorylation

All four nucleosome histone tails contain acceptor sites (serine, threonine, and tyrosine residues) that can be phosphorylated by many protein kinases and dephosphorylated by phosphatases. In mammalian cells, phosphorylation of histones H1, H2B, H3, and the histone variant H2AX plays a crucial role in gene expression regulation, mitosis, and DNA repair [8]. Histone phosphorylation is prominently involved in various cellular processes associated with chromatin remodeling and gene expression. Abnormal histone phosphorylation has been reported in many types of cancers such as colorectal, prostate, and breast cancer [9].

Somatic amplifications of mitogen and stress-activated kinase 1 and 2 (MSK1/2) have been detected in colorectal, prostate, and breast cancers. The inhibition of MSK1/2 reduces cancer cell proliferation *in vitro* and tumor development *in vivo*. MSK1/2 can specifically phosphorylate H3 S10 and S28 at the promoter regions of FOS and JUN genes, which can then activate their transcription and promote tumorigenesis [10-13].

During mitosis, H3S10ph and H3S28ph of the whole chromosomes are mediated by Aurora B kinase (AURKB), and this is essential to maintain chromosome stability. Dysregulation of AURKB is related to high aggressiveness and poor prognosis in colorectal cancer [14,15].

Histone ubiquitination

It has been shown that H2A, H2B, and H3 can be ubiquitination targets associated with DNA repair, gene transcription and genome integrity. Ubiquitination of H2AK119 leads to gene suppression in mammalian cells, while ubiquitination of H2BK123, which is catalyzed by RNF20 and RNF40, is linked with transcription activation, such as the activated expression of tumor suppressor p53. It has been reported that there is a global loss of H2Bub1 in colon, ovarian, lung, and parathyroid cancers [16,17].

Histone methylation

Histone methylation is one of the key markers in histone modifications that occur at both arginine and lysine residues on the tails of histone proteins H3 and H4. By adding one, two, or three methyl groups to certain amino acids, the transcription of a certain gene can be either activated or repressed [18]. Methylation states are usually regulated by two enzyme families: Histone Methyltransferases (HMTs) and Histone Demethylase (HDMs). HMTs consist of two families: Histone Lysine Methyltransferases (HKMTs) and Protein Arginine Methyltransferases (PRMTs). In addition, dysregulation of histone methylation and mutational inactivation or overexpression of specific methyltransferases are linked to the pathogenesis of various types of cancer [19-22].

HKMTs: Most HKMTs possess a Su(var)3-9, enhancer of Zeste, trithorax (SET) domain, except for DOT1L protein [23]. HKMT proteins can be classified into the following subgroups: SET1, SET2, suppressor of variegation (SUV39), SET and MYND domain-containing (SMYD), enhancer of zeste homolog (EZH), PR domain (PRDM), and other SET domain-containing proteins. Notably, MLL, EZH2, SETDB1, SMYD, NSD1, SETD2, and DOT1L have been identified as functional oncogenic drivers in gastrointestinal tumorigenesis.

MLL: Mixed lineage leukemia 1 (MLL-1), also known as histone-lysine N-methyltransferase 2A (KMT2A), is a HKMT that catalyzes the methylation of H3K4 and acts in opposition to polycomb repressive complex proteins [24]. MLL-1 genetic events, particularly gene fusion and overamplification, have been shown to be important characteristics of leukemia. Frame shift mutations of MLL genes and loss of expression of MLL3 protein are common in gastric and colorectal cancers with high microsatellite instability [25].

EZH2 and EZH1: EZH2 and EZH1, two members of the EZH family of HKMTs, mediate H3K27 methylation and transcription suppression in the form of a multi-subunit protein complex polycomb repression complex 2 (PRC2), a protein complex that involves both a K-methyltransferase and "reader" proteins that recognize H3K27me3. In cancer cells, H3K27me3 has also been demonstrated to repress many gene expressions [26]. EZH2 is upregulated both at the transcriptional and protein level in many human cancers and promotes cancer cell proliferation, invasion, and metastasis [27-29].

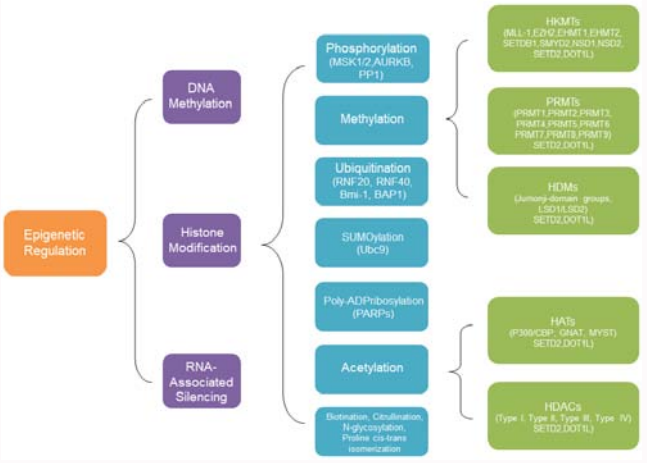

Figure 1: Histone modifications and associated histone-modifying enzymes that have been reported in tumorigenesis.

EZH2 expression is also associated with survival in colorectal cancer patients treated with anti-EGFR therapeutics [30]. Silencing EZH2 inhibits colorectal cancer cell proliferation, significantly reduces the CD133+/CD44+ subpopulation, decreases expression of self-renewal-related genes, and strongly impairs tumor-initiating capacity [31]. At present, several EZH2 small molecular inhibitors have been developed, one (EPZ6438) of which is assessed in phase 1/2 clinical trials for B-cell lymphoma or advanced solid tumors [32].

SETDB1: SETDB1, a histone methyltransferase that plays a critical role in early development, methylates histone H3 on lysine 9, up to tri-methylation (H3K9me3). SETDB1 is located within a melanoma susceptibility locus and facilitates melanoma formation. SETDB1 is also frequently amplified in other tumor types, such as liver and lung cancer [33,34]. In colorectal cancer, SETDB1 mediates APAK repression under hypoxia by an increase in H3K9me3 along the APAK loci, and facilitates hypoxia-induced p53-dependent apoptosis [35].

SYMD: SYMD subfamily includes 4 members (SMYD1, SMYD2, SMYD3, SMYD4) and is characterized by a split SET domain that does not have definite substrate specificity. SMYD2 methylates H3K4 and H3K36, while H3K4, H4K5, and H4K20 are the targets of SMYD3. Both of these are over-expressed in gastro colorectal and hepatocellular carcinomas and promote cancer cell proliferation [36-41]. Over expression of SMYD3 is relevant to increased STAT3 activation in gastric cancer [39]. Smyd3 binds H3K4Me3-modified histone tails, which facilitates its recruitment to the core promoter regions of a particular set of genes [40]. It was found that in the development of lung adenocarcinoma and pancreatic ductal adenocarcinoma, Ras/Raf/MEK/ERK signaling was activated by the methylation of the lysine 260 of the MAP3K2 gene by SMYD3 [42].

NSD1: NSD1 belongs to the SET2 subfamily of HKMTs, mediating H3K36 dimethylation. It was found that in AML, NSD1 tends to be combined with nucleoporin-98 to form a fusion protein in the recurring t(5;11)(q35;p15.5) genomic translocation. Several oncogenic genes including HoxA7, HoxA9, HoxA10, and Meis1 can be transcriptionally activated by this fusion protein [43]. It has been reported that a mononucleotide repeat (A7) in the coding sequence of NSD1 can be a target for a frame shift mutation in cancers with Microsatellite Instability (MSI), such as gastric and colorectal cancers [44].

SETD2: SETD2 is the H3K36 trimethyltransferase and plays an important role in gene transcription elongation and mismatch repair by interacting with RNA polymerase II in cells. SETD2 mutations have been detected in many human tumor cells including GI stromal tumors, renal, bladder and breast carcinomas, and high-grade gliomas [45,46]. While H3K36me3 epigenetically marks actively transcribed genes, which play a role in DNA repair, chromatin structure modulation during elongation, and stem cell regulation, SETD2 may represent a novel tumor suppressor gene, which contributes to tumor progression. The existence of SETD2 mutations in a number of human tumors suggests that disruption of the SETD2-H3K36me3 pathway is a distinct epigenetic mechanism for tumorigenesis, thereby providing a new target for the development of cancer diagnostics and therapeutics [47-52]. According to our unpublished data, expression of SETD2, together with H3K36me3, was remarkably reduced in colon cancer tissues, and conversely associated with tumor progression and patient survival. It was also reported that the depletion of SETD2 activated Wnt/β-catenin signaling through the modulation of alternative splicing, which could then contribute to the development of colorectal cancer [53].

DOT1L, a HKMT without a SET domain, which specifically mono-, di- and tri-methylates H3K79, is involved in colorectal cancer, leukemia, and dilated cardiomyopathy [54]. DOT1L is necessary for hematopoietic malignancies owing to oncogenic fusion proteins MLL-AF10 and CALM-AF10, among others, and activates the Wnt pathway through binding TCF4 and β-catenin, which are Wnt transcription factors [32,55,56]. Inhibitors of DOT1L have demonstrated promising therapeutic effects in preclinical colorectal cancer treatment [57]. One of the inhibitors, EPZ-5676, which can catalyze the mono-, di- and tri-methylation of H3K79, is now in clinical trials for MLL-rearranged leukemia [58].

PRMTs: Many PRMTs are associated with different types of cancers. For instance, PRMT1 constitutes the majority of arginine methylations of the PRMT family and specifically mediates di-methylation of H4R3 [19]. In gastric tumors, PRMT1 is associated with a poor prognosis and relapse after adjuvant chemotherapy. Moreover, PRMT1 is a promising therapeutic target for treating refractory gastric tumors [59]. Additionally, PRMT5 mRNA levels are significantly higher in gastric tumors than the corresponding adjacent normal tissues and PRMT5 enhances the malignant phenotype of gastric cancer cell lines. It may serve as a biomarker for patient stratification and a potential target for therapy [60]. PRMT5 is also over expressed in colorectal cancer cell lines and patient-derived primary tumors, correlated with increased cell growth and reduces overall patient survival. PRMT5 regulates the levels of H4R3me2s and H3R8me2s methylation on FGFR3 and eIF4E promoters, leading to a decrease in their expression [61]. In addition, other PRMTs, including PRMT2 and PRMT6, are overexpressed in colon, gastric, breast, and lung cancers [62].

HDMs: Histone methylation markers can be removed by a variety of enzymes, with markers at specific histone tail residues interacting with distinct histone lysine demethylases (K-demethylases). K-demethylases can be divided into 2 classes: Lysine-specific demethylase 1 or 2 (LSD1/KDM1A and LSD2/KDM1B) and Jumonji (JmjC)-domain groups.

Lysine-specific demethylase 1 or 2: Lysine-specific demethylase 1 or 2 is highly expressed in many tumors, including colorectal, prostate, lung, and breast cancers, as well as neuroblastomas, and

is associated with a poor prognosis [63]. LSD1 is a K-demethylase that targets H3K9 and H3K4 methylation which has recently shown to be overexpressed in estrogen receptor-negative breast cancer, mesenchymal tumors, and bladder cancers [64-67]. In solid tumors, LSD1 knockdown is shown to inhibit cell proliferation of several cancer cells [32]. Deletion of LSD1 leads to a reduced colorectal cancer cell proliferation. It has also been implicated in targeting p53 and DNMT1 (DNA methyltransferase 1), downregulating the expression of CDH-1 by epigenetic modification, and consequently promoting metastasis of colon cancer cells [68,69].

Although more researches are needed to further understand the functional consequences of dysregulation of histone methylation, it is clear that K-demethylases and K-methyltransferases play important roles in gastrointestinal tumorigenesis and could be novel targets for cancer therapy. Several inhibitors of LSD1 have been used in clinical trials, including TCP and GSK2879552, which are aimed at treating AML and MDS [58].

Histone acetylation

Unlike histone methylation, histone acetylation is associated with transcriptional activation since it occurs on lysine residues and is believed to neutralize the charge of positively charged histones, thereby decreasing their interactions with negatively charged DNA, thus enhancing transcription [70]. Histone acetylation plays an important role in transcription activation, cell cycle regulation, and DNA repair. An imbalance between histone acetylation and de-acetylation has been observed in various cancer types, leading to aberrant gene expression of oncogenes and tumor suppressors. Histone acetylation is generally achieved by Histone Acetyltransferases (HATs), which consist of three distinct families: Cyclic AMP Response Element-Binding (CREB) protein (p300/CBP), Gcn5-related Acetyltransferases (GNAT), and MOZ, Ybf2/Sas3, Sas2, Tip60 (MYST) [70]. HATs from each of these families have been shown to play a role in tumorigenesis. A variety of cancers including stomach, colon, lung, and endometrial cancers have mutations in histone acetyltransferases [71].

HATs

P300/CBP: P300/CBP is capable of acetylation of all four core histones [72,73]. Loss of heterozygosity at either p300 or CBP has been detected in many cancer cell lines as well as colon, gastric, cervical, and breast cancers [72,74-79]. PCAF expression is down-regulated in gastric cancer samples and is correlated with tumor invasion, tumor size, and node metastasis stage [80]. Many proteins, including p53, β-catenin, Myb, Myc, and HIF-1, can interact with P300/CBP, which regulates the expression of their downstream target gene [81].

GNAT

Out of the known pathways involved in cancer, the Wnt signaling pathway, commonly dysregulated in tumorigenesis, has been shown to be augmented by the HAT GCN5 in breast cancer [82,83]. In cancer cells, Gcn5 co-activates the expression of oncoprotein E2F1, Myc, cyclin D1, and cyclin E, promoting cell proliferation and tumor growth [84-86]. GCN5 also activates downstream target gene expression by interacting with Myc or E2F1. In human colon cancer development, GCN5 plays a positive role and its suppression in cells with E2F1 over expression can further facilitate cell apoptosis [87].

P300/CBP-Associated Factor (PCAF), also known as lysine acetyltransferase 2B (KAT2B), is another GNAT family acetyltransferase and specifically acetylates the histone H3K9 residue. Both PCAF mRNA and protein are down regulated in gastric cancer cells, which correlates with a poor survival rate. By interacting with AE1 and p16, PCAF inhibits gastric tumor growth, promoting ubiquitin-mediated degradation of AE1 and p16 translocation into the nucleus [88].

MYST

MYST family HATs have been found to be dysregulated in Acute Myeloid Leukemia (AML), which form fusion proteins including MOZ/CBP, MYST4/CBP, MORF/CBP, and MOZ/p300. Tip60, a member of the MYST family, regulates the proliferation, invasion, and migration of cancer cells, as well as metastasis, which is down regulated in various types of cancers, including colon, gastric, lung, and prostate cancers [89-93].

HDACs

Histone deacetylation has been identified as an early step in tumorigenesis [94]. Early loss of monoacetylation of histone H4K16 was found in a mouse model of multistage skin carcinogenesis. Additionally, a number of cancer cell lines were found to be hypoacetylated, suggesting that histone deacetylation is a widespread event in cancer [70]. HDACs are a class of enzymes that can antagonize acetylation and have multiple substrates involved in many biological processes, including proliferation, differentiation, apoptosis, and other forms of cell death. In humans, HDACs have been identified and divided into Type I (HDAC1/2/3/8), Type II (HDAC4/5/6/7/9/10), Type III (sirtuins), and Type IV (HDAC11), based on their homology to yeast HDACs. The role of HDAC is complex at different stages of cancer, although there have been some HDAC inhibitors approved for T-cell lymphomas treatment.

It has been reported that in gastric, colorectal, prostate, and many other cancers, HDACs are overexpressed, which is linked to a poor prognosis [95-97]. However, in normal cells, HDACs are reported to play tumor-suppressing roles. In gastric tumors, HDAC1 suppression up regulates CRADD expression and HDAC1 directly binds to the CRADD promoter to suppress the viability of gastric cancer cells [98]. In 2008, Godman et al. also found that long-term knockdown of HDAC3 led to the inhibition of β-catenin's translocation to the nucleus in cancer cells [99,100]. HDAC3 can also be recruited to the RUNX2 promoter by CBX4, which inhibits colorectal tumor cell migration and invasion [101]. Over expression of HADC1, HADC2, HADC3, HADC5, and HADC7 have been reported in colon cancer, linked with the down regulation of genes in the Wnt signaling pathway, while HADC4 and SIRT1 are down regulated [102]. It was reported that SIRT1 acted as a tumor suppressor in gastric cancer through the inhibition of NF-κB signaling [103].

The pattern of HDAC deregulation in cancer cells has provided a novel epigenetic target for cancer treatment-the HDAC inhibitors-which have been widely adopted in the treatment of a number of diseases. Currently, suberoylanilide hydroxamic acid (vorinostat), romidepsin (Istodax), and belinostat (beleodaq) have been approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma (SAHA and romidepsin) and peripheral T-cell lymphoma (belinostat and romidepsin) [104]. At present, more HDAC inhibitors are under investigation at different stages of clinical trials, such as resminostat, which is aimed to treat colorectal cancer and is currently under the second phase of clinical trials [102].

Other histone modifications

Histone Poly-ADP-ribosylation plays various roles in chromatin

structure modulation, DNA repair, and cell division [105,106]. This process is mediated by Polymers of ADP-ribose Polymerases (PARPs). The dysfunction of PARPs has been found in multiple cancers, including colon, breast, laryngeal, and prostate cancers. By inhibiting the DNA repair pathway, PARP antagonists enhance the sensitivity of cancer cells to radiation and chemotherapies.

Until now, it has not been functionally demonstrated whether other types of histone modifications, including SUMOylation, biotination, citrullination, and proline isomerization, are involved in gastrointestinal tumorigenesis. Further studies are required to elucidate their roles.

Conclusion

In this review, we described in detail the roles of histone modifications and the related enzymes involved during gastrointestinal tumorigenesis. It has been proven that histone modifications result in malignant transformation through changes in chromatin structures, by regulating oncogenes, or in tumor suppressor expression. The dynamic equilibrium of these modifications and their effects play key roles in gastrointestinal tumorigenesis. Aberrant histone modifications, as well as the associated enzymes, have been widely linked to tumorigenesis. Histone-modifying enzymes have been the targets of therapeutic agents that are either approved for cancer treatment or which are currently under development in clinical trials. However, we still lack an understanding of the histone modifications involved in gastrointestinal tumorigenesis. Further investigations on the mechanisms of epigenetic alterations and their impacts on gastrointestinal tumorigenesis will help identify novel therapeutic targets and offer new therapeutic choices for cancer treatment in the future.

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