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Review Article

The Impression of Histone Modification and DNA Methylation in Gastric Cancer Development: Molecular Mechanism Approach

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The epigenetic alterations like histone modifications , DNA methylation and others remarkable categories including nucleosome remodeling and RNA mediated targeting have been strongly investigated recently .In this way , beside the notable importance of DNA methylation ,the histone modifications are the most important issues in the tumorogenesis and cancer progression. Moreover, the fluctuations of histone modifications particularly, the dysregulation of histone alterations is engaged directly in carcinogenesis. Conclusively, it is confirmed that aberrant epigenetic modifications along side with chromosomal losses and mutations are involved in cancer progression. Hence, histone modifications and DNA methylation have the impressive abilities and potential to be practical prognostic biomarkers in order to manage all aspects of cancers like diagnosis, controlling and treatment. In this review article, we focus the recent advances of these alterations specially, histone modifications in gastric cancer development.

Keywords: Histone modifications, gastric cancer, DNA methylation, epigenetic

Gastric cancer is one the most crucial and serious cancers and is divided into two main types: intestinal and diffuse (1, 2). It is a multi-factorial disease caused by many exogenous and endogenous pathological parameters, as well as many genes (3). In this way, epigenetic factors like DNA methylation and histone modifications play a very important role in carcinogenesis. In this review article we classified some main epigenetic changes with their molecular mechanism and their important pathways like DNA methylation, histone accetylation, histone methylation , histone phosph-orylation and others related categories.

DNA Methylation

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DNA methylation is a notable and vital regulator of gene expression and may occur as hypo or hypermethylation (4).The methylation of the 5-carbon on cytosine in CpG dinucleotides was the first explained covalent alteration of DNA and is certainly the most wildly specialized alteration of chromatin. In this way, DNA methylation was initially declared within telomeres, repeated sequences, centromeres and inactive X-chromosomes (5). Remarkably, hypomethylation is usually seen in malignant cells and epigenetic changes in all kinds of cancers are the methylation modifications that happen within CpG islands, playing a notable role in transcriptional regulation and consequent malignant transformation (4). It is approved that between 5%–10% of unmethylated CpG promoter islands become methylated in various cancer genomes abnormally. Moreover, CpG hypermethylation of promoters not only influence the expression of protein coding genes but also the expression of different noncoding RNAs that some of them have a remarkable role in malignant transformation (5). Significantly, genome-wide DNA methylation researches have also revealed attractive modifications in DNA methylation within gene structures. Indeed, recent researches have formed that many actively transcribed genes have high levels of DNA methylation within the gene structure, advising that the combination and spatial spreading of DNA methylation is indispensable in transcriptional regulation (6).

Considerably, three active DNA methyltransferases have been distinguished in advanced eukaryotic cells. DNA methyltransferase 1 is a permanent methyltransferase that identifies hemimethylated DNA produced during DNA replication (7). On the contrary, DNA methyltransferase 3a and DNA methyltransferase 3b, have the potential of *de novo* methylation and are able to create DNA methylation during embryogenesis (8). Evidently, DNA methylation prepares a structure for many methyl-binding proteins. These combination comprise MBD3, MECP2, MBD1, and MBD2 which are essential to employ histone-modifying enzymes to manage the chromatin-templated functions (9).

It is obvious that, the mutations in DNA methyltransferases and also MBD proteins have long been known to contribute to developmental disorders (10).

Significantly, these mutations are consistently heterozygous and are anticipated to confuse the catalytic function of these enzymes (11). Consequently, histone modifications, histone methylation and histone phosphorylation are so impressive and involved in cancer development..

Histone Modifications

Histone modifications have a practical and impressive effect on the regulation of transcription and particularly in all DNA- template processes (12). Notably, the wide differences in histone modifications offer a considerable complex that is gradually starting to be clarified. It is necessary to mention that the cellular enzymes that alter histones may also have nonhistone consequences.

Histone acetylation

Histone acetylation has an important role in healthy physiological functions (13). Correspondingly, the most important and vital enzymes to conserve the balance between acetylation and deacetylation are histone acetyltransferases and histone deacetylases, respectively. Relatively, according to their cellular location and operations, histone acetyltransferases could be ranked into two main types: Type A which it is located in nucleus, and also reveals activity on gene transcription regulating. Relatively, type B is located in cytoplasm and catalyzes acetylation of some nonhistone proteins. So, histone acetyltransferases significantly comprise TIP60,YBF2, SAS2, MYST,

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GNAT, MOZ, CBP and p300 families (14, 15). Interestingly, all these families occur in structural combinations like CBP, p300 , PCAG, MORF and GCN5. These structures interact and affect each other closely and notably they can play significant roles in differentiation, cell cycle and cell development (16, 17).

Recently, histone deacetylases have been ranked into four main classes; class I contains 1, 2, 3, 8; class II contains 4-7, 9, 10; class III comprises SITR1-7; and class IV comprises histone deacetylase II, which includes some features of classes I and II (18). Relatively, histone deacetylase I strongly regulate histone acetylation and chromosomal combinations. Correspondingly, histone deacetylase II and IV certainly catalyze nonhistone deacetylation in the cytoplasm (19, 20). The members of SIRTs family regulate cell situation, cell cycle and also DNA repair (21). Consequently, the active section of nucleosomal histone is continually under hyper-acetylation and the acetylation is associated to gene activation, while deacetylation mechanism is active in gene silencing process (22, 23).

Histone methylation

Histone proteins are classified into five main classes: H1, H2A, H2B, H3, and H4. Correspondingly, methylation locations are often discovered in lysine or arginine of H3 or H4 structures (24). Conspicuously, histone methyltransferases comprise histone arginine methyl transferases and histone lysine methylation

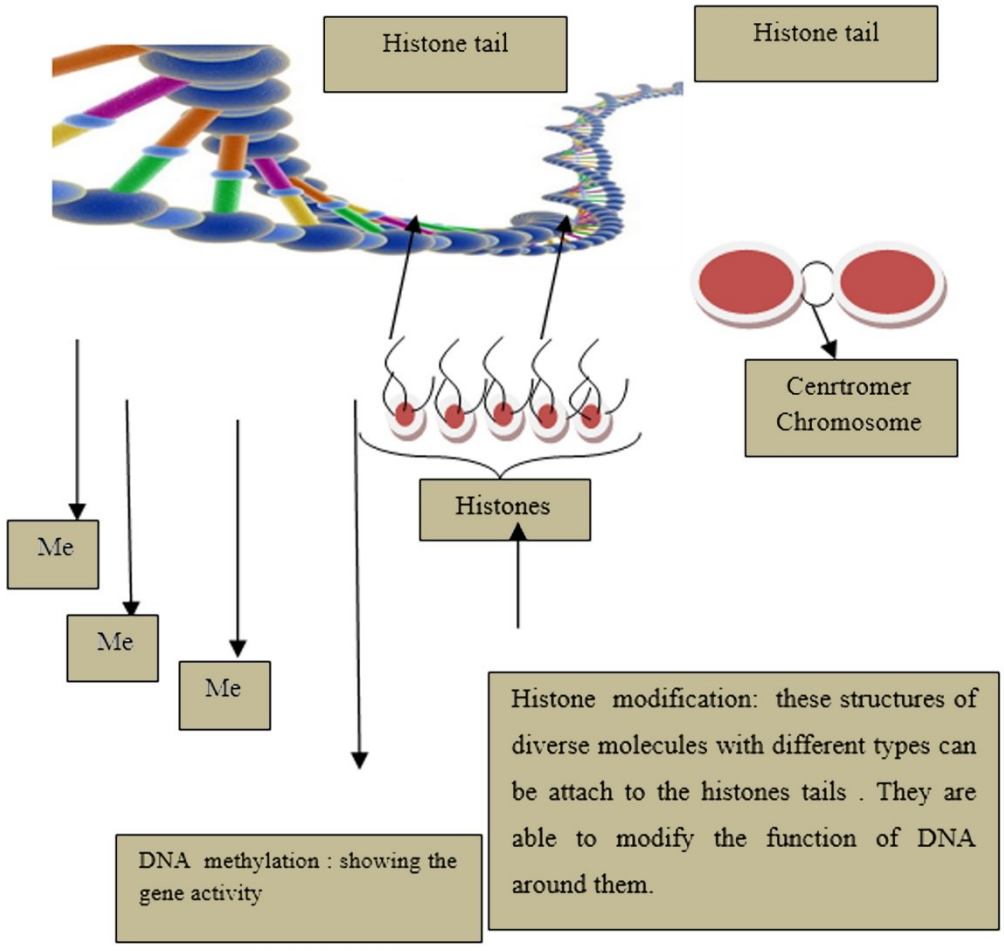

Figure 1. The coordination and correlation of DNA methylation and histone modification as epigenetic factors which are involved in cancer progression.

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transferases. Moreover, histone arginine methyl transferases include two main kinds: kind I catalyzes arginine with single methylation and asymmetric double methylation structures and kind II catalyzes arginine with single or double methylation structures (25, 26). Histone methylations were confirmed to be one of the main reversible programs, specially like acetylation. Numerous amount of histone demethylases were distinguished, including JMJD2, KDM4 and JHDM1A (26) . Conclusively, the two main components of the epigenetic code (histone modification and DNA methylation) have an important interaction with each other in cancer development (Figure1).

Histone phosphorylation

Histone phosphorylation is a reversible alteration which often occurs in threonine, tyrosine and serine (27). The histone phosphorylation modifies chromosome combinations and remarkably regulates their interaction alongside with transcription factors to influence gene transcription (28). Phosphorylations with different types are associated with eclectically cellular functions like mitosis, DNA repair, transcription, and apoptosis. Phosphorylated regions were recognized like: S10,S28,T3,T11, and T45. The serine, threonine and tyrosine of H2B, H4, H1,and H2A were also found to be phosphorylated completely . This phosphorylated functions are catalyzed by different kinases. Considerably, histone phosphorylation strongly regulates gene transcriptions in compatible and suitable signaling pathways (29).

The correlations and coordination among different types of histone modifications

The histone modifications are engaged in gene activation and alongside with dependent inhibition. For instance, H3 S10 phosphorylation improves H3K14 acetylation and also the methylation of H3K4. Forthermore, it can inhibit the methylation of H3K9 and also H2BK123 ubiquitination (30, 31). Hence, the methylation of H3K9 bands the phosphorylation of H3S10 and remarkably the gene transcription, whereas, the acetylation of H3K9 is associated with transcription function. Conspiciously, histone modifications are associated to epigenetic factors like DNA methylation and histone modification and they can participate to silence some antitumor genes (32, 33).

Table 1. Histone modifications models in different cancers. Many researches have demonstrated that histone modifications can anticipate the prognosis of eclectic cancers, particularly in cancers of digestive system

Cancer type	Histone modifications
Stomach	H3K27me3, H3K9me3
Esophagus	H3K18ac, H4R3me2, H3K27me3
Prostate	H3k4me1, H3k4me2 H3K9me2, H3K9me3, H3k27me3, H4K20me1, H4K2Ome2, H3K18ac, H3Ac, H4Ac
Liver	H3k4me3, H3k27me3
Pancreas	H3k4me2, H3K9me2, H3K18ac

The effect and role of histone modification in gastric cancer development

Histone modification was shown to influence significanlyt physical activities. So, its dysregulation can cause abnormal gene expressions to modify their physiological operations, leading to carcinogenesis (34, 35). In this way, histone modification affect the functions of normal cell, particularly in cancers of digestive system (Table 1).

The effect and role of histone acetylation in gastric cancer development

Many researches in histone acetylation on malignant tumor have shown it's direct effect in gastric cancer (36, 37). Obviously, some tumor suppressor genes like CIP1,P21 and WAP1 with low amounts of H3 acetylation on promoter

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concluded in down-regulation. Similarly, it H. pylori infection increases the expression of some genes like CIP1, P21 and WAP1 by preserving high acetylation amounts of H4 on it's specialized promoter regions. It is illustrated that histone H4 has a slight impact on acetylation in digestive system.

Furthermore, the relationship of acetylation with invasion, lymphatic metastasis and tumor stage was confirmed (38). Remarkably, it was also shown that HDAC4 can accelerate gastric cancer development by P21 repression (39).

The effect and role of histone methylation in gastric cancer development

The studies on histone methylation in gastric cancer strongly concentrated on histones 3 and 4 (H3,H4) (40). In this way, it was shown that the triple methylation on H3K9 was directly related with lymphovascular invasion, overall survival rates, tumor stage and recurrence. Correspondingly, it was confirmed that there were 128 main genes totally with remarkable changes in H3K27 methylation structure on CpG islands between normal and cancerous cells. These events can contribute to explain this mechanism in gastric cancer development. Relatively, it was shown that low amount ofH3K9 di-methylation, DNA methylation and H3K9 acetylation in the promoter regions of P16 tumor suppressor gene will reduce the expression of P16 (41, 42).

The effect and role of histone phosphorylation in gastric cancer development

There is less investigation in histone phosphorylation in gastric cancer. Interestingly, the presence of high amounts of H3 phosphorylation was confirmed in gastric cancer (43). Moreover, the H3 phosphorylation is practical and necessary for the anticipation of prognosis in gastric cancer and it is related with vascular invasion ,lymphatic metastasis and histological types. Remarkably, H. pylori can reduce the phosphorylation amounts of H3S10 and H3T3 for regulating the cell cycle (44).

Micro RNAs (miRNAs) and gastric cancer

One of the effective geneticfactors on cells function modifications and also in increasing the danger of cell intering to growth phase, changing the

Table 2. Some microRNAs involved in cancers of digestive system. The most effective miRNAs in development of digestive cancers development are cited

Types of cancers	Increased expression	Decreased expression
Gastric- Intestinal	miR-106b-25	miR-15b, miR-16
Colorectal	miR-18, miR-224 miR-10a, miR-17-92 cluster, miR-21, miR-24-1, miR 29b-2 miR-31 , miR- 96, miR -135b, miR-183	miR-143, miR-145, Let-7, miR 30-3P, miR-124a, miR- 129, Mir 133b, miR-328
Esophagus	miR-194, miR-192, miR -200c, miR-21	miR-203, miR-205
Pancreas	miR-221, miR-376a, miR-301, miR-21, miR-24-2, mir-1000, miR-103, miR-107, miR-125b-1, miR-155, miR-181, miR-106, miR-363, miR- 301, miRa, miR-212, miR-34a376	miR-375, Let-7, miR-200, miR200b
Hepatocellular	miR-18, miR-21, miR-33, miR-130b, miR-135a, miR-221, miR-224, miR-301	miR- 199a/b, miR-195, miR-200a/b, miR-214, miR-223, miR-125a, miR-122a, miR-101, Mir-139, miR-150, miR-26a, miR-101

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Table 3. Some miRNAs and their targets in cancers of digestive system (54-57)

Types of miRNA	The miRNA's disorder in different cancers	The target molecules of miRNAs
Mir18-a	Increasing in gastric cance4	PIAS3
mir-25	Increasing in gastric cancer	LATS2
mir-101	Increasing in gastric cancer	MCL1
mir-122	Decreasing in hepatocellular carcinoma	Cyclin G1, P53
mir-143	Decreasing in colorectal cancer	KRAS
Mir-145	Decreasing in colorectal cancer	EGFR, IGF-1R
Mir-512-sp	Decreasing in gastric cancer	MCL1

expression of controlling growth genes and proliferation of cells, are micro RNAs (miRNAs) (45, 46).

Micro RNAs are new known factors of gene expressions regulation which alter the range of different proteins production in post transcriptional phase with affecting the stability of mRNAs (47, 48). Correspondingly, miRNAs are a group of small RNAs with regulatory role which can be connected to the 3' untranslated region (3'UTR) in each mRNA and can increase or decrease the stability of mRNAs (49, 50). According to the type and function of proteins for which miRNAs are connected to mRNAs and change their expression, miRNAs can act as tumor suppressor or oncogene (Table 2) .

Besides of this issue, the expression of miRNAs is also different in different cancer types (51- 53). The sequences of miRNA and the sequence of their attachement in the 3'UTR on each mRNA can affect the risks of diseases development. Noticeably, recent studies have shown that the miRNAs with the code miR-18a acts as an oncegene and also increases the risk of stomach adenocarcinoma development with effecting the expression of protein Inhibitor of activated signal transducer and activator of transcription 3 (PIAS3) protein (54). Table 3 summarizes some important miRNA involved in digestive system cancer development and their principal target(s) (54-57).

Conclusion

Histone modifications and DNA methylation are significantly involved in gastric cancer. Evidently, they are parts of epigenetic alterations and have remarkable roles in tumorogenesis and carcinogenesis (58-60). Histones modifications and DNA methylation depend on each other not only in different types of cancers, but also in all types of genetic and epigenetic functions and cellular processes (61-64). Correspondingly, knowing and finding molecular causes of cancers specially giving full attentions to these epigenetic factors, can lead to early diagnosis and even treatment.

Conflict of interest

The authors declared no conflict of interest.

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