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Recent Advance of Histone Modification in Gastric Cancer : A Review

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Abstract: *Epigenetics play important roles during development progress of tumor. The histone modifications are the most important constitutedfield. Recently, accumulating research focused on exploring the roles of those modifications in regulating tumorigenesis. Moreover, the dysregulation of histone modifications is supposed to have vital clinical significance. Numerous histone modifications have the potential to be prognostic biomarkers, monitoring response of therapy, early diagnostic markers. Herein, we review the recent advances of histone modifications involving development of gastric cancer.Gastric cancer (GC) is one of the most frequent tumors in the world. Stomach adenocarcinoma is a heterogeneous tumor, turning the prognosisprediction and patients' clinical management difficult. Some diagnosis tests for GC are been development using knowledge based in polymorphisms, somatic copy number alteration (SCNA) and aberrant histone methylation. This last event, a posttranslational modification that occurs at the chromatin level, is an important epigenetic alteration seen in several tumors including stomach adenocarcinoma. Histone methyltransferases (HMT) are the proteins responsible for the methylation in specific amino acids residues of histones tails. Here, were presented several HMTs that could be relating to GC process.*

Keywords: Acetylation, gastric cancer, histone modification, methylation, phosphorylation.

I. INTRODUCTION

The occurrence and development of tumorare resulted from genetic and epigenetic dysregulation.[1□3]Genetic variations, such as gene mutation, translate, transpositions, are always recognized as the principal factor of tumor development. Accumulating evidence demonstrated that the epigenetic changes caused by the microenvironment also played important roles.[4,5] The epigenetic is referred to the changes of heritable gene expression and regulation without sequence rearrangement.[6] At present, DNA methylation, histone modification, genomic imprinting, chromosome remodeling, miRNAs are known as epigenetic changes. Among those events, high methylation of CpG islands in the promoter of tumor suppressor genes is the most common.[7] Moreover, some epigenetic changes are associated with chromosome, of which are core histone proteins modification (namely histone modification). The principal of histone modification is that the N terminus of core proteins (H2A, H2B, H3, H4) are modified with multiple covalent modification after translation, such as acetylation, methylation, and phosphorylation.[8]As the discovery of a large number of histone modification enzymes and the proposed of "histone codon",[9]histone modification is suggested not only to regulate normal physiological function, such as DNA replication, translation, or repair, but also to involve in tumor development. In view of this, more and more attentions had been focused on histone modification. Numerous studies have explored the changes in multiple kinds of cancer, such as prostatic cancer, lung cancer, renal cancer,breast cancer, ovarian cancer, and pancreatic cancer.[10,11] More importantly, those changes indicated pivotal clinical significance. In addition, a lot of the catalytic enzyme of histone were found to have high activities in tumor.[11] Gastric cancer was ranked as the top morbidity and mortality rates. The investigations on gastric cancer histone modification would promote understanding the mechanism of gastric cancer development.[3] Moreover, those effects would improve diagnosis or therapy of gastric cancer. In this review, we conclude and discuss the recent progress of histone modifications involving development of gastric cancer.

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II. MAIN MODIFIERS OF HISTONE METHYLATION IN DIGESTIVE CANCERS KMTs

KMTs are a group of enzymes that catalyze mono-methylation, di-methylation, or tri-methylation by adding one, two, or threemethyl groups, respectively, from S-adenosyl-L-methionine to theε-amino group of a histone lysine residue, thus regulating gene expression. For example, H3K27me3 (trimethylation of lysine 27 of histone 3) is often associated with transcriptionally repressed chromatin, and H3K4me3 is often linked to transcriptionally active chromatin. According to their defined protein domain or homologous sequence, KMTs are classified into eight distinct subfamilies: KMT1–8.[12] A cluster of KMTs, including the H3K36 methyltransferase KMT3A,[13]the H3K9/56 methyltransferase G9a (also called KMT1C),[14]the H3K27 methyltransferase enhancer of zeste homolog 2 (EZH2, also called KMT6A),[15,16] and the H3K4 methyltransferases KMT3E,[17,18]KMT2A,[19,20]KMT2D,[21] etc., has been found to be ectopic expressed in digestive cancers. Among these KMTs, EZH2, a catalytic subunit of polycomb repressive complex 2 (PRC2),[22] is one of the most commonly reported methyltransferases that represses gene expression in digestive cancers via H3K27me.[23]

III. CHROMATIN STRUCTURE

Eukaryotic chromosome is complex and constituted with DNA, histone, nonhistone molecules. There are two basic forms, heterochromatin that exist in condensed chromosome with transcription inhibited, and euchromatin that was the loos chromosome with active transcription.[24] The basic units of chromatin are nucleosome, core granules are composed of histone octamer (core histones), which contains two H2A, H2B, H3 and H4, and about 146 bp DNA that intertwined on the core histones. Furthermore, the core histones would interact through H1 to form chromatin. Every core histone contained a spherical domain and an exposed N terminal. After finishing histone translation, the N terminal would be modified with acetylation, methylation, phosphorylation, ubiquitination, sumoylation, adenosine diphosphate (ADP) glycosylation, or carbonylation Fuchs *et al*.[25] Histone modifications can regulate structures andfunctions of chromosome by two ways. Firstly, histones areenriched with positively charged arginine and lysine, which can tightly bind to DNA with a negative charge. Thus, histone modifications would affect the interaction between DNA and histone. Secondly, histone modification prone to produce binding surface of protein recognized motif. It recruited special protein complex to the binding surface. Thus, histone modification could determine active or inactive of chromosome by changing its structures, as results, to control cellular physical pathways.

IV. HISTONE METHYLATION

Histone modifications leading to gene expression alterations have been described in several cancer types, but the methylation status of chromatin is still unclear for GC. Using the ChIP-on-chip technique, Zhang *et al*[26] identified candidate genes with significant differences in H3K27me3 in GC samples compared to adjacent nonneoplastic gastric tissues. These genes included oncogenes, tumor suppressor genes, cell cycle regulators, and genes involved in cell adhesion. Moreover, these investigators demonstrated that higher levels of H3K27me3 produce gene expression changes in *MMP15*, *UNC5B,* and *SHH*.

In 2011, Kwon *et al*[27] showed that *LAMB3* and *LAMC2* were overexpressed in GC samples in comparison with non-neoplastic adjacent tissue samples. Furthermore, these researchers demonstrated that overexpression of these genes was a result of the enrichment of H3K4me3 in the gene promoter. Using immunohistochemistry, Park *et al*[28] showed that higher levels of H3K9me3, which is a repressive mark, was associated with higher T stage, lymphovascular invasion, and recurrence in gastric tumors. They also observed that the level of H3K9me3 was correlated with patient survival, because stronger methylation corresponded to a worse prognosis and intermediate methylation to an intermediate prognosis. Taken together with results from previous studies, these results have suggested that histone methylation results in a worse prognosis by inactivating certain tumor suppressor genes[29,30]. Moreover, Li *et al*[31] used GC cell lines to demonstrate that the PRC1 member CBX7 initiated trimethylation of H3K9 at the *P16* locus through recruitment and/or activation of the HMT SUV39H2 to the target locus. This finding links two repressive epigenetic landmarks, H3K9me3 formation and PRC1 binding within the silenced domains in euchromatin, and builds up a full pathway for epigenetic inactivation of *P16* by histone modifications. Recently, Angrisano*et al*[32] reported that *H. pylori* infection is followed by activation of *iNOS*gene expression, chromatin changes at the *iNOS*promoter (including

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decreased H3K9 methylation and increased H3K4 methylation), and selective release of MBD2 from the *iNOS*promoter in a GC cell line.

V. METHYLATION INHIBITOR DRUGS

The silencing of cancer-related genes by DNA methylation and chromatin modification are reversible and may represent a viable epigenetic therapeutic target. In the last decade, drugs that modify chromatin or DNA methylation status have been used alone or in combination in order to affect therapeutic outcomes[33]. Specially, cytosine analogs (5-azacytidine and 5-aza-2'- deoxycytidine) are powerful mechanism-based inhibitors of DNA cytosine methylation. These cytosine analogs are incorporated into the DNA of replicating cells after the drugs have been metabolized to the appropriate dNTP. After incorporation into the DNA, the analogs interact with DNA methyltransferases to form covalent intermediates, and this interaction inhibits DNA methylation in subsequent rounds of DNA synthesis[34].Both drugs have been approved by the US Food and Drug Administration for use in hematological malignancy treatment[35].

In GC, surgery remains the primary curative treatment for gastric tumors. Currently, adjuvant and neoadjuvant therapies are accepted[36];however, so-called

epigenetic therapy has not yet been used in treatment of GC patients.

In the past few years, epigenetic screening techniques using treatment with a demethylating agent have been developed to identify genes with epigenetic aberrations in GC cell lines. Zheng *et al*[37]treated a GC cell line with 5-aza-2'-deoxycytidine and performed DNA methylation array analysis of these cells with six normal mucosal samples from healthy patients. These results revealed 82 hypermethylatedgene promoters. These authors investigated 15 candidate genes by methylation specific PCR and confirmed five highly methylated promoters: *BX141696*, *WT1*, *CYP26B1*, *KCNA4,* and *FAM84A*. All of these, except *FAM84A*, also showed DNA hypermethylationin serum of GC patients, suggesting that serum DNA offers a readily accessible bioresource for methylation analysis. A similar study conducted by Jee*et al*[38]described 11selected genes and validated the genes in three GC cell lines and in non-neoplastic gastric tissue by bisulfate sequencing. Differential DNA hypermethylation was observed in *GPX1*, *IGFBP6*, *IRF7*, *GPX3*, *TFPI2,* and *DMRT1* promoter regions in GC cells but not in non neoplastictissues. Moreover, a poor survival rate was observed in those individuals with higher methylation status at the *TFPI2* gene. *TFPI2* is a serine protease inhibitor,which negatively regulates the enzymatic activities of trypsin, plasmin, and a tissue factor complex. Therefore, it has been proposed that this gene inactivation may be implicated in human carcinogenesis and metastasis[39].

VI. HISTONE ACETYLATION

Histone acetylation is a reversible process of dynamic balance in healthy physiological process. Histone acetyltransferase (HATs) and histone deacetylase (HDACs) are the most important enzymes to maintain balance between acetylation anddeacetylation. According to cellular location and functions, HATs could be divided into two types: Type A in the nucleus, which exhibits function on regulating gene transcription; while, type B in cytoplasm catalyzes acetylation of nonhistone proteins. HATs mainly include GNAT, MYST, MOZ/YBF2/SAS2/ TIP60 and CBP/p300 families. All these three families exist in complexes forms, such as GCN5, PCAG, MORF, CBP/p300. The complexes would interact and effect each other. Thereby, those interactions could play important roles in cell development, differentiation, or cycles. Currently, HDACs are divided into four Class from I–IV; I includes 1, 2, 3, 8; II includes 4–7, 9, 10; III includes SITR1□7; IV includes HDAC11, which contains some characteristics of I and II.[40] HDACs I mainly regulate histone acetylation and chromosome structures; HDACs II and IV probably catalyze nonhistone deacetylation in the cytoplasm.[41]The histone acetylation is the process that HATs transfer acetyl from acetyl coenzyme A to the specific e□amino of Lysresidual in the amino terminal of core proteins. The positive charge is removed, while DNA molecular with a negative charge is in favor of unfolding the DNA conformation and loosening nucleosome. Furthermore, the loosened structurepromotes the interaction between transcription factors orsynergy transcription factors and DNA chains. Thereafter, thehistone acetylation activates specific gene transcription. Onthe contrary, HDAC could remove the acetyls from histone Lysand recover the positive charge, thus the positively charged Lysincrease the attraction between negatively charged DNA chainand histone, preventing transcriptional regulatory elementsbinding to promoters and inhibiting the transcription. Ingenerally, the active region of nucleosomal histone is

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alwaysunder hyper□acetylation. Therefore, the acetylation is relatedto gene activation while deacetylation means gene silence.[42,43]

VII. HISTONE PHOSPHORYLATION

Histone phosphorylation is adding PO4 residual to terminus of histone. This reversible modification often happened in serine, threonine and tyrosine. The histone phosphorylation changes chromosome structures and regulates the interactionwith transcription factors to affect gene transcription. Aswell as, different phosphorylations are related with variouslycellular process such as transcription, mitosis, apoptosis, DNA repair. Up to now, the histone H3 phosphorylation has been extensively explored. Moreover, series of conservative phosphorylated regions were identified (such as T3, S10, T11, S28, T45). The serine, threonine and tyrosine of H1, H2A, H2B and H4 were also prone to be phosphorylated. The phosphorylated processes are catalyzed by various kinases. For instance, DNA damage signaling pathways induce histone H2AX to be phosphorylated and which mainly dependent on triphosphate inositol kinase related kinase.[44]Mst1 kinase could catalyze phosphorylation of H2BS14, which play important roles in cell apoptosis.[45] The transcription activation related phosphorylation of histone H3S10 and
H3S28 were catalyzed by Aurora kinase.MSK/RSK/Jil□1 kinase family could mediate H3S10 phosphorylation to regulate gene expression.[46] Regarding to function, histone phosphorylation mainly regulates gene transcriptions inrelated signaling pathways. Mahadevan*et al*.[47] found that
the fast phosphorylation of H3 always accompanied with activation of c□fos and c□jun in 1991. After that, more and more evidence demonstrated that the phosphorylation of H3 Ser10 played extremely important roles during activating transcription in eukaryotes.[46]Protein kinase A can mediate H3 phosphorylation on serine 10, which is associated with transcriptional activation of ERK□mitogen□activated protein kinase (MAPK) signaling pathway and c□fos.[48]Indirectly immune location assays also proved that ERK□MAPK pathway could result in multiple sites H3 phosphorylation, among of them, some phosphorylated H3 might associate with quick activations of genes involving in ERK□MAPK pathway.[49] In addition, H3 Ser10 phosphorylation can initiate cellular mitosis and promote chromatic aggregation at early G2 stage.[50□51]

VIII. THE CLINICAL APPLICATION OF HISTONE MODIFICATION

Similar with other epigenetic, the histone modificationswere reversible progresses, providing principle evidencefor tumor□targeted therapy. So far, accumulating studiesemphasized on histone deacetylation and methylation inhibitors, such as trichostatin A (TSA), SAHA, and DZNep, BIX□01294.[52□56] Among them, SAHA had been approved by US Food and Drug Administration to apply in clinical for the treatment of cutaneous T□cell lymphomas.[56]During carcinogenesis and development, various epigenetic modifications interacted with catalytic enzymes. The designed inhibitors on a series epigenetic modifications showed adverse effects in the treatment of tumors. For instance, DNA methylation inhibitors 5□aza, 5□aza□dC and etc., are insufficient in specificity and stability *in vivo*, with unsatisfactory clinical benefits. Although HDAC could induce tumor cell cycle arrest, differentiation, or apoptosis. Moreover, some agents, such as TSA, SAA, MS□275, have been tested in phase I and II clinical trials.[53,57□61] However, HDAC shows nonsignificantlydifference in comparing with DNA methylation inhibitors. Therefore, combined application of multiple inhibitors has become a hot□topic for the clinical investigations of histone
modification inhibitors. It is reported that combined DNMT and HDAC inhibitors could activate expression of tumor repress genes, including MLH1, TIMP3, CDKN2B, CDKN2A, and ARHI, promoting tumor cell apoptosis.[62□66] Manuyakorn*et al*.[67] found that the pancreatic cancer patients with low levels di□methylation of H3K4, H3K9, and acetylation of H3K18 were not benefit from 5□fluoouracil (5□FU) chemotherapy. It is supposed that the combination of acetylated and methylated inhibitors might improve histone acetylation and thus improve prognosis of patients with pancreatic cancer. Histone modification could be served as biomarkers for
prognosis, therapy response and others.[68].

IX. CONCLUSION

In a word, histone modifications were part of epigenetic and attracted a lot of attention on its roles in carcinogenesis and tumor development. However, the clinical application of histone modifications was limited in overall levels of

modification. Until now, the clinical application value of some specific promoter histone modifications still undefined. In addition, malignant tumor was disease with obviously heterogeneity. Thus, it still need to be extensively explored the roles of histone modification.

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