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Review Article

SCENARIO OF EPIGENETIC ALTERATIONS AND GASTRIC CANCER-A REVIEW

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ABSTRACT

Gastric cancer is believed to be result of the accumulation of multiple genetic alterations resulting in either oncogenic over expression or loss of tumor suppressor gene function. Epigenetic alterations as a crucial mechanism to silence the variety of methylated tissue-specific and imprinted genes have been extensively studied in gastric carcinoma and have been found to play important roles in gastric carcinogenesis and as a result epigenetics has become a hot topic for research, whereby genetic markers are bypassed and research on reversible epigenetic events, such as methylation and histone modifications that play a crucial role in carcinogenesis is need of the day. Epigenetic alterations, including DNA methylation, histone modification, loss of genome imprinting, chromatin remodeling and non-coding RNAs, have been found to be associated with human carcinogenesis. Detection of epigenetic changes has been applied in the clinics to stratify risk in cancer development, detect early cancer and predict clinical outcomes as epigenetic changes including altered DNA methylation are reversible and are used as targets for cancer therapy or chemoprevention. As per literature a number of recent studies reported DNA methylation level to be a useful biomarker for diagnosis, risk assessment and prognosis prediction for gastrointestinal (GI) cancers. This review briefly discusses the basic aspects of epigenetics.

INTRODUCTION

Rather than merely a perpetuating mass of dysregulated cells growing in an uncontrolled manner, the cancer is also defined by the dynamic genetic and epigenetic alterations that contribute to its initiation and progression (1). Epigenetic alterations mostly DNA methylation, Histone modifications and altered microRNAs expression, can regulate gene expression through mechanisms other than changes in basic genomic DNA sequence. A large number of recent studies have confirmed that gastric cancer is a multistage pathological state and involves gradual accumulation of various genetic and epigenetic alterations, leading to gain-of-function in oncogenes and loss-of-function in tumor suppressor genes (2-5). Genetic anomalies, such as p53, KRAS, PIK3CA, ARID1A, MLL3 and MLL mutations as well as PIK3CA, C-MET, ERBB4 and CD44 amplifications are frequently found in gastric cancer suggesting that they may be key tumorigenic events and may play a critical role in gastric tumorigenesis (6-11).

Pathogenesis of gastric cancer

The pathogenesis of gastric cancer presents a classical example of gene-environment interactions and among the environmental factors, diet and infection with H. pylori are the most common causes of gastric cancer. Aberrant gene expression also plays an important role in gastric carcinogenesis (4, 12). The oncogenic activation of β-catenin and K-ras has also been found in gastric cancer (13) and in addition amplifications of the c-erbB2 and c-met genes have each been found in approximately 10% of the cases. Among the tumor suppressor genes, p53 mutations have been reported in both the diffuse and intestinal type of gastric cancer. Mutations in APC are frequently observed in gastric adenomas and are rarely found in gastric cancers (15). Somatic mutations of Ecadherin gene are mostly observed in sporadic diffuse type gastric cancer (33-50%) (16). Runtrelated transcription factor 3 (RUNX3) has been found to play role in gastric cancer, although mutations in this gene are rare (17) and microsatellite instability (MSI) is observed in 5-10% of diffuse type gastric cancer and in 15-40%

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of intestinal type of gastric cancer (15). In addition to these well characterized genetic changes, epigenetic alterations, including promoter CpG island hypermethylation are the most common molecular alterations in human neoplasia especially in gastric cancer (18). Promoter hypermethylation of mismatch repair gene hMLH1 is the main mechanism responsible for MSI in gastric cancer and the hypermethylation of p16 is common in gastric cancer with a higher incidence in the intestinal type. However mutations of the p16 gene are infrequent in gastric cancer (19). Thus, the present review focuses on the specific epigenetic alterations in various genes that are commonly observed in gastric cancer.

Epigenetics

'Epigenetics' term was coined by Conrad Waddington in 1939 (20) to describe 'the casual interaction between genes and their products. Riggs et al defined epigenetics as 'the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence (21). In present scenario present the meaning of the term 'epigenetics' has broadened to include heritable and transient/reversible changes in gene expression that are not accompanied by a change in the DNA sequence. The critical role of epigenetic modifications in human diseases is also coming to the fore front and becoming apparent, and in future hope that it may be the path for control of cancer (18).

Epigenetic modifications

The comprehensive knowledge of epigenetics has contributed to the understanding of different biological activities, such as DNA methylation, chromatin structure, transcriptional activities and histone modification. Two most important epigenetic changes include DNA methylation and chromatin remodeling (18, 22) among which chemical change in DNA methylation in the DNA sequence occures most commonly at the cytosine moiety of CpG dinucleotides while as chromatin remodeling occurs through histone modifications and ultimately affect the interaction of DNA with chromatin-modifying proteins. It has been found that DNA methylation and histone modifications are associated with the silencing of critical tumor suppressor genes and the activation of oncogenes involved in cancer (3, 18, 22). The poor prognosis associated with gastric cancer is due to the detection of the tumor at a late stage thus the hunt for novel molecular markers is imperative for the early detection and prognostic prediction of this disease. The use of novel chemotherapeutic agents targeting these newly identifiable molecular markers may further improve the prognosis and life span of patients with gastric cancer. Various genetic markers till date have been used for the early detection of tumors, prognostic prediction as well as with the aim to elucidate the genetic pathway of gastric carcinogenesis (15, 23). However in recent years, epigenetic markers have gained popularity of particular importance is promoter hypermethylation which has various advantages over genetic markers. Promoter hypermethylation is much more common than genetic alterations in cancer and it occurs in the defined region of a gene in all forms of cancer as compared to a wide range of mutational variations in a specific gene. Thus, the detection of promoter hypermethylation as an epigenetic change may be an efficient and cost-effective method for tumor detection (24, 25).

DNA methylation and epigenetic gene silencing

Gastric cancer is most frequently diagnosed cancer and in current scenario it is second leading cause of cancer-related deaths in the world. Based on microscopic observations there are two subtypes intestinal and diffuse based on histological basis and tumor growth pattern, which differ widely in molecular pathogeneses (26-27, 2). Nonetheless, epigenetic alterations like promoter hypermethylation play important roles in the development of both gastric carcinoma types. DNA methylation being a reversible chemical modification of cytosine in the CpG islands of promoter sequences and is catalyzed by a family of DNA methyltransferases does not alter the genetic information, but only alters the readability of the DNA and results in the inactivation of a gene by subsequent transcript repression (28). This type of modification plays a critical role in the control of cellular process, including embryonic development, transcription, X-chromosome inactivation and genomic imprinting (29). CpG dinucleotides not frequently observed throughout the human genome are present at 20% of their expected frequency and approximately half of the human gene promoter regions have CpG‑rich regions of 0.5-2 kb in length where the CpG dinucleotide frequency is higher than expected and these CpG-rich sequences are often known as CpG islands (30). Almost 94% of CpG islands remain unmethylated in a normal cell. However, some subgroups of CpG island promoters are methylated, such as in tissue and germ line-specific genes. In general, CpG island methylation is associated with gene silencing and also recruits histone deacetylases and other factors involved in transcriptional silencing (18). The changes in the DNA methylation status in cancer cells is a complex phenomenon involving global hypomethylation and localized hypermethylation in which global hypomethylation of the genome was initially considered to be an exclusive event in cancer development (24). The methylation loss in cancer is mainly due to the hypomethylation of repetitive DNA sequences (LINE and SINE) and the demethylation of inotropic sequences and during the development of a neoplasm, the degree of hypomethylation of genomic DNA increases as the lesion progresses from a benign one to a metastatic one (18, 31). This DNA hypomethylation has been suggested to be involved in the development of cancers by three ways. First it increases genomic instability, secondly it reactivates transposable elements and thirdly it leads to the loss of gene imprinting. The demethylation can favour mitotic recombination, leading to deletions, translocations and chromosomal instability (18). The abnormal activation of oncogenes due to promoter demethylation (hypomethylation) has yet not been established (31) and the exact association between global hypomethylation and the development of cancer remains to be consolidated (18). Contrary to this the inactivation of tumor suppressor genes through the hypermethylation of CpG islands within promoter regions is a major event in carcinogenesis (18) and the hypermethylation of CpG islands has a silencing effect on miRNAs in cancer (32, 33). Gene promoter hypermethylation of many candidate genes such as CDKN2A, CDK2AP2, CDH1, MGMT, RASSF1, RUNX3, DLC1, ITGA4, ZIC1, PRDM5, PCDH10, TFPI2, RUNX3, SPINT2, BTG4, SFRP2, hMLH1, DKK-3, TCF4, GRIK2, RAR, RASSF1A, LRP1B and SFRP5, has been

reported to be associated with gastric cancer development (34, 35, 2).

Histone modifications

Basic histones are evolutionarily highly conserved proteins with a characteristic accessible aminoterminal tail and a histone fold domain mediating interactions between histones to form the nucleosome scaffold (18). The N-terminal of histone polypeptides are extensively modified by more than 60 different posttranslational modifications mostly methylation, acetylation, phosphorylation, ribosylation, ubiquitination, sumoylation, carbonylation and glycosylation (18, 22, 36). In normal cells, a delicate balance maintains nucleosomal DNA in either an active that is acetylated or an inactive that is deacetylated form and this balance is controlled by acetylating enzymes e.g., histone acetyltransferases (HATs) and deacetylating enzymes e.g., histone deacetylases (HDACs). In addition other modification includes methylation of arginine and lysine residues of histones. Pertinently methylation is catalyzed by histone methyltranferase (HMT) and the process is involved in the regulation of a wide range of gene functions and chromatin modeling and remodelling. Generally, lysine methylation at H3K9, H3K27 and H4K20 is associated with gene silencing while as methylation at H3K4, H3K36 and H3K79 is associated with gene activation (22). These epigenomic changes in the pattern of CpG methylation may in turn lead to global changes in histone modification patterns in multiple human cancers. Changes in histone modification patterns independent of CpG methylation have also been directly linked to cancer development and progression. Additionally histone modifications have also been implicated in DNA replication, repair and condensation (18).

Mechanisms of epigenetics

Epigenetic alterations such as histone modifications, DNA methylation, chromatin remodelling and even changes in noncoding RNAs including miRNAs together govern the epigenome code. Such epigenetic events in the genome are important during normal development and differentiation (37). Importantly, it has been found that gene expression profiles change during cellular differentiation according to not only a network of transcription factors but also the "epigenomic landscape" of the cell. Histone methylation mostly occurs on lysine (K) and arginine (R) residues and these methylation marks serve as docking sites for histone reading factors (38). However, both lysine and arginine methylation can occur on both histones and non-histone proteins. The highly conserved histone lysine methylation occurs at mono-, di-, and tri-methylation levels and these modifications are commonly associated with gene activation or repression, depending on the target histone modification. Important to mention here is that histone H3 lysine 4 (H3K4), histone H3 lysine 36 (H3K36), and histone H3 lysine 79 (H3K79) are associated with gene activation whereas histone H3 lysine 9 (H3K9), histone H3 lysine 27 (H3K27) and histone H4 lysine 20 (H4K20) are associated with gene repression. The N-terminal tails of histones also undergo other post-translational modifications that play significant roles in various DNA-templated processes, including transcription (37-39). Three main mechanisms have been found through which DNA methylation suppresses gene transcription (40, 41). The first involves methyl-CpG-binding domain (MBD)-mediated gene silencing. Various methyl-CpG-binding proteins (MBPs) have been found and identified including methyl-CpG-binding protein 2 (MeCP2) and MBD1, MBD2, MBD3 and MBD4. These proteins posses a transcriptional repressor domain involved directly in repressing transcription. Also, MBDs can recruit transcriptional co-repressors, such as HDACs and Sin3A to methylated DNA that also aid in repression (3, 41). The deacetylation event of histone results in closed or repressed chromatin configuration, which in turn leads to the exclusion of transcription factors and allele-specific gene silencing. The second mechanism of gene silencing is mediated through DNMTs including DNMT1, DNMT3A and DNMT3B which have a transcription repressor domain and can thus directly suppress transcription and in addition, these DNMTs can recruit co-transcriptional repressors, such as HDACs to methylated DNA identical to MBDs. The third mechanism is that CpG island hypermethylation can sterically prevent the binding of activating transcription factors to gene promoter region (3, 24).

Epigenetic alternations in gastric cancer

Most of the traditional molecular studies on gastric cancer have focused on identifying genetic mutations causing cancer or on tumor suppressor genes (39, 42, 43). However, with the advancement more studies are now focusing on the discovery of novel biomarkers that are epigenetically silenced in early carcinogenesis (44-46). It has been found that almost half of the tumor suppressor genes that causes familial cancers through mutations are also inactivated or silenced by promoter hypermethylation in sporadic cancers (36). Increasing evidence suggests that epigenetic events play a key role in cancer development and progression. It has become apparent that different tumor types have a different profile or clustering of gene hypermethylation referred to as the CpG island methylator phenotype (CIMP). The CIMP group was identified as having tumor-specific DNA methylation and clearly distinguished due to exhibiting a higher methylation index in comparison to non-CIMP tumors that show only low levels of tumor-specific methylation (16). Tumors with concurrent hypermethylation in multiple loci have been defined as CIMP-high (CIMP-H) and CIMP plays an important role in the progression of gastric cancer. Concurrent hypermethylation of gene promoters is associated with MSI in gastric cancer with the CIMP‑H phenotype as depicted in one of the study (47). This study demonstrated that the concordant methylation of multiple gene/loci found in 31% of tumors was associated with an improved survival, but was not an independent predictor of prognosis for patients with gastric carcinogenesis and thus the prognostic role of CIMP status in gastric cancer is unclear (19). Silencing of p16 (INK4a) by promoter region hypermethylation has also been reported in gastric cancer and the hypermethylation of p16 may predict the malignant potential of dysplasia and the early diagnosis of cancer (48). CDKN2A promoter methylation has also been reported in 30% of gastric cancer cases (3,19,49) and the CDKN2A hypermethylation may contribute to the malignant transformation of gastric precursor lesions (50). The promoter hypermethylation of hMLH1 has also been found to be a frequent event in gastric cancer and is associated with the loss of hMLH1 expression in the majority of gastric cancers exhibiting MSI (19, 51-53). The promoter hypermethylation of the DNA repair protein O6-

methylguanine DNA methyltransferase (MGMT) has been found in 31% of gastric cancer cases (54). The cancer cells have ability to migrate and invade other organs using vascular channels and is characterized by a variety of genes, such as APC, E-Cadherin (CDH1), H-Cadherin (CDH13) and FAT tumor suppressor cadherin (3, 22). CDH1 promoter hypermethylation has been found in 54.8% of analyzed cases of sporadic gastric cancer (55) and in 28.6 of cases, the downregulation of E-cadherin may be associated with a poor prognosis of Gastric cancer (56). It has also been reported that H. pylori infection is associated with E-cadherin methylation, leading to the downregulation of E-cadherin and hence reduced expression (57). The promoter region hypermethylation of the TSP1 gene has been observed in 33% of cases of gastric cancer (58). The deleted in liver cancer (DLC-1) gene has been found to be hypermethylated in 30% of cases of primary gastric carcinoma patients (59). The aberrant promoter region hypermethylation of COX-2 has also been observed in gastric cancer (60, 61). Aberrant promoter region hypermethylation of many genes like CASP8, hMLH1, CDH1 and MDR1 have been found to be involved in gastric cancer (62). Lee et al reported the promoter aberrant methylation of DAPK, E-cadherin, GSTP1, p15 and p16 promoters (63). Kang et al investigated and found the aberrant methylation of multiple genes in gastric cancer tissue, gastric adenoma, intestinal metaplasia and chronic gastritis (64). Similar results were depicted by Oue et al at the CpG island of the p16 (INK4a), CDH1 and RARβ promoters and the study depicted that the hypermethylation of the p16 (INK4a) promoter was more common in intestinal type than in diffuse type gastric cancer (65). CDH1 and RARβ aberrant promoter hypermethylation has been frequently found in the diffuse scattered type of gastric cancer (3). Hypomethylation also contributes to gastric carcinogenesis and the demethylation of melanoma antigen (MAGE), synucleingamma (SNCG) and cyclin D2 has been observed in gastric cancer (19). Also MAGE expression is known to be activated by promethylation and the demethylation of both the MAGE-A1 and A3 promoters are more frequently observed (29 and 66%, respectively) in the advanced clinical stages of gastric cancer and are also associated with a poor prognosis (66). SNCG demethylation has been found to be common in cases with LN metastasis (67). The hypomethylation of the cyclin D2 promoter was observed in 71% of cases of gastric cancer and is more common in stage III and IV tumors than in stage I and II tumors (68). The modification of histone by methylation, which occurs at lysine or arginine residues, is generally associated with inactivation or silencing of the respective genes (69-73). Also, histone modifications regulate genes that participate in various stages of the cell cycle. It has also been reported that methylation of histone H3 plays an important role in carcinogenesis by silencing tumor suppressor genes and hence leading to their reduced expression (74, 75). Park et al observed global histone modification patterns using immunohistochemistry and reported that the trimethylation of H3K9 positively correlates with tumor stage and lymphovascular invasion in gastric carcinogenesis (69). On the other hand, the acetylation of histone, which occurs mostly at lysine residues of N-terminal domains, is known to be associated with transcriptional activation and has been shown to be associated with a poorly differentiated or diffuse type of histology (3, 69). Histone H4 acetylation is reduced in gastric cancer compared to normal mucosa and the reduction correlates with a more advanced stage, deeper invasion and a greater extent of LN metastasis (76) and has also been reported to be associated with reduced tumor suppressor gene p21WAF1/CIP1 expression in gastric cancer (77). Increased expression of p21 (WAF1) induced by H. pylori has been found to be associated with the release of HDAC-1 from the p21 (WAF1) promoter and the hyperacetylation of histone IV (3, 78).

Clinical implications of epigenetics

The research on epigenetic alterations could be very useful for cancer diagnosis and treatment. CpG island hypermethylation can become one of the most promising biomarkers for the early diagnosis of tumor as the aberrant promoter hypermethylation occurs very early during carcinogenesis (79). This epigenetic event may prove to be more beneficial than genetic studies, as promoter methylation occurs more frequently in tumors than genetic alterations in general and also due to the fact that several methylated loci may be analyzed simultaneously. Since promoter hypermethylation is seen within a well defined region of a gene and hence epigenetic studies are more efficient and cost-effective. The overall survival rate for patients with cancer is very poor and the early detection of lesions and/or reliable biomarkers for monitoring locoregional recurrence may increase the survival of patients with cancer (3, 25). Epigenetic changes especially promoter region hypermethylation in tumors may also be utilized in predicting tumor behaviour or prognosis of cancer (56).

Implications of epigenetics in gastric cancer

The histone H3 at K9 has been found to be trimethylated in gastric cancer which is associated with an advanced tumor stage and lymphovascular invasion and the acetylation of histone H3 at K9 has been found to be present in the poorly differentiated or diffuse type of histology (3, 70). The recent development in the knowledge of relevant gene silencing by epigenetic alterations in cancer development is closely linked to epigenetic drug design and drug development. These epigenetic events function in three important ways like DNA cytosine methylation, histone modification and nucleosomal remodeling (3, 80, 81). Similarly, CDH4 gene methylation has also been found at a high frequency in gastric cancer cases and may be an early event in tumor progression. The hypermethylation of DAPK gene as observed in the intestinal, diffuse and mixed type of gastric cancer correlated with the presence of LN metastasis, an advanced stage and poor survival (48, 49). Methylation at CpG sites is observed in 95% of cases of RASSF1A non-expressing primary gastric cancer and the loss or downregulation of RASSF1A correlated with the advanced stage and advanced grade of gastric tumors. In a similar study, epigenetic silencing of the XAF1 gene by aberrant promoter methylation has been reported in gastric cancer (50, 51). In primary gastric cancer, methylation specific PCR of TSPYL5 has showed hypermethylation at the CpG island in most of the cases (53). Similarly, the downregulated expression of SFRP2 has been shown to be correlated with promoter hypermethylation in most of cases of primary gastric cancer (56). Nojima et al has also found a high frequency of CpG island methylation in SFRP1, SFRP2 and SFRP5 in both gastric cell lines and primary gastric cancer (57) while as Oshimo et al detected the hypermethylation of the SOCS-1 gene in 44% (33/75) of cases of gastric cancer. The

hypermethylation of the SOCS-1 gene was found to be associated with the decreased expression of the SOCS gene in an advanced tumor stage (60). AKAP12/gravin is one of the A-kinase anchoring proteins (AKAPs) which functions as a kinase scaffold protein and dynamic regulator of the β2 adrenergic receptor complex and the hypermethylation of two forms of the AKAP12 gene (AKAP12A and AKAP12B) has been obsedved in gastric carcinogenesis (61). The aberrant promoter hypermethylation of the retinoblastoma protein-interacting zinc finger gene (RIZ1), has been reported in 69% of cases of gastric cancer and 21% of cases of non-neoplastic mucosa. This gene is involved in chromatin-mediated gene expression and is also a target for frame shift mutation in cancers with the MSI phenotype (62). In similar study, Kim et al found RUNX3 methylation in 8% of cases of chronic gastritis, 28% of cases of intestinal metaplasia and in 27% of cases of gastric adenoma (65). The promoter hypermethylation of retinoic acid receptor β (RARβ) was observed in 64% of cases of gastric cancer (66). The use of DNA methylation inhibitors provides an attractive approach for the treatment of cancer, as the toxicity of these drugs to normal cells is potentially lower than that of conventional anticancer chemotherapeutic agents (16). DNA methylation inhibitors are divided into nucleoside and nonnucleoside analogues while the former form a covalent intermediate complex with DNMT, preventing the cell from being methylated correctly. DNMT inhibitors like 5-azacytidine (Vidaza) and 5-aza-deoxycytidine (decitabine) are the only two cytidine analogues that have been approved by the US Food and Drug Administration (FDA) for haematological malignancies (92-93) and the non-nucleoside analogues have an advantage over the nucleoside analogues since they bind to the catalytic site of the enzyme DNMT and are not integrated into the DNA thus avoiding the non-specific interactions of nucleoside analogues (13). Hydralazine which is a potent peripheral vasodilator, is currently also used as demethylating agent in cervical cancer (94). HDAC inhibitors are divided into four groups like short chain fatty acids, hydroxamic acids, cyclic tetrapeptides and benzamides (13). The hydroxamic acid, trichostatin A (TSA) has been shown to be a chemosensitizer which enhances the efficacy of chemotherapeutic drugs in gastric cancer and TSA is a promising chemotherapeutic agent in combination with 5-fluorouracil, paclitaxel and irinotecan in gastric cancer cells (95). Previously in October 2006, the FDA approved the first HDAC inhibitor, vorinostat (SAHA) for the treatment of cutaneous T cell lymphoma (96) and various other HDAC inhibitors are currently undergoing clinical trials (97, 98). Another novel method for the application of epigenetics in the treatment of cancer is the reactivation of key enzymes controlling the cellular response to anticancer drugs. Satoh et al (99) demonstrated that microtubule inhibitors, such as docetaxel and paclitaxel induce apoptosis in gastric cells with fork head-associated and ring finger (CHFR) methylation and found that gastric cancer cells not expressing CHFR lack a mitotic checkpoint and are highly susceptible to microtubule inhibitors. Thus, CHFR methylation may be a useful molecular marker to predict the responsiveness of gastric cancer to treatment with microtubule inhibitors. Koga et al also reported CHFR methylation in predicting the response of microtubule inhibitors in the treatment of gastric cancer (100). Epigenetics could potentially be used in the future as a tool for the discovery of power full screening markers for the early detection of gastric cancer. Epigenetic studies may also be used as a risk assessment tool for the identification of persons at higher risk of developing cancer and can also be used in clinical practice to predict tumor behavior and for the prognosis of patients with gastric cancer, as well as for the identification of biomarkers to monitor the response to therapeutic agents. The other application of epigenetics could be in therapy and the DNA methylation inhibitors along with HDAC inhibitors may be exploited as monotherapy or in combination with other anticancer drugs for the treatment of gastric cancer.

CONCLUSION

- Epigenetics could be used in future as a tool for the discovery of potential screening markers for the early detection of many types of cancers.
- Epigenetic studies may also be used as a risk assessment tool for the identification of individuals who are at higher risk of developing cancer.
- Epigenetics may also be used in clinical practice to predict tumor response and for the prognosis of patients with gastric cancer, as well as for the development of biomarkers to monitor the response to chemotherapeutic agents.
- Epigenetics can also find application in therapy and DNA methylation inhibitors and HDAC inhibitors may be used as monotherapy or in combination with other anticancer drugs for the treatment of gastric cancer.
- Epigenetic signatures have a high potential usefulness in early diagnosis, screening, monitoring and prediction of prognosis or therapy responses for cancer patients.
- Further investigation in this field would through light on more epigenetic alterations of GI cancer and thus help us to develop novel therapeutic strategies for GI cancers.

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