Epigenetic modulation associated with carcinogenesis and prognosis of human gastric cancer (Review)

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Abstract. Gastric cancer (GC) is a leading cause of cancer-related death, particularly in Asia. Epidemiological and other clinical studies have identified an association between a number of risk factors, including *Helicobacter pylori*, and GC. A number of studies have also examined genetic changes associated with the development and progression of GC. When considering the clinical significance of the expression of a specific gene, its epigenetic modulation should be considered. Epigenetic modulation appears to be a primary driver of changes in gastric tissue that promotes carcinogenesis and progression of GC and other neoplasms. The role of epigenetic modulation in GC carcinogenesis and progression has been widely studied in recent years. In the present review, recent results of epigenetic modulation associated with GC and their effects on clinical outcome are examined, with particular respect to DNA methylation, histone modulation and non-coding RNA. A number of studies indicate that epigenetic changes in the expression of specific genes critically affect their clinical significance and further study may reveal epigenetic changes as the basis for targeted molecular therapy or novel biomarkers that predict GC prognosis or extension of this often fatal disease.

Contents

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1. Introduction

Gastric cancer/carcinoma (GC) is a relatively common cancer, particularly in Asia (1). Although its incidence is decreasing gradually in developed countries, high morbidity and mortality of GC remains among cancer types (2,3). Early GC may be treated, and even completely cured surgically, using endoscopic mucosal resection and endoscopic submucosal dissection (4,5). However, the prognosis of advanced or distantly metastasized GC is worse. Although a number of systemic chemotherapy regimens are available to treat unresectable or distantly metastatic GC, highly advanced GC is difficult to completely cure using chemotherapy. Therefore, prevention or early detection of this fatal disease is critical. The epigenetic aspects of GC are an important current frontier in understanding its development and progression, and identifying its earliest stages.

Epidemiology and other clinical research have identified an association between several risk factors and GC. *Helicobacter pylori* is an influential factor in the carcinogenesis of GC (6). Certain dietary characteristics, including high sodium intake or low produce consumption are recognized risk factors for GC (7,8). Many studies have also examined genetic changes related to GC development and progression. Whole human genome sequencing has been available since 2003, and has led to new insights into human diseases, including the genetic aspects of GC (9); both genetic and epigenetic changes have been demonstrated to orchestrate carcinogenesis and progression of neoplasms.

Notably, genetic and epigenetic changes have been identified to affect cancer development in a stepwise manner, although they may have limited effects separately. Epigenetic modulation, including DNA methylation status, histone modification and non-coding RNA modulation, greatly influences neoplastic development (10). Therefore, understanding how these epigenetic changes affect GC has importance in detecting, treating and preventing this fatal disease. In the present review, epigenetic modulation of GC in terms of its association with epidemiological factors and clinicopathological factors is outlined, and the clinical significance of

epigenetic modulation in GC carcinogenesis and prognosis is summarized.

2. DNA methylation

Specific and genome-wide DNA methylation. Abnormal DNA methylation can be caused by internal and external factors, and is distributed in two general patterns, genome-wide hypomethylation and site-specific CpG island local hypermethylation (11,12), which affect the prognosis of GC and other types of cancer. The methylation status of a gene's promoter region may determine whether or not it acts as a tumor suppressor; promoter regions of various tumor suppressor genes have been independently associated with prognosis of GC (13-20) (Table I).

The effect of whole-genome hypomethylation on GC was first described in 1996 (21). In that study, the authors identified that hypomethylation of DNA was increased in a stepwise manner in normal gastric mucosae, superficial gastritis and atrophic gastritis, but did not significantly increase between atrophic gastritis and GC. The European Prospective Investigation into Cancer and Nutrition cohort study identified that global demethylation of tumor cell genomes occurred in GC, which is consistent with the idea that abnormal hypermethylation of specific genes occurs concomitantly with genome-wide hypomethylation (22). Long interspersed element 1 (LINE-1), a retrotransposon, occupies ~17% of human DNA; its hypomethylation is hypothesized to be a surrogate for whole-DNA hypomethylation. Bae *et al* (23) demonstrated that LINE-1 hypomethylation was an independent prognostic factor following curative resection for advanced GC. Shigaki *et al* (24) also identified an association between LINE-1 hypomethylation and shorter survival time in GC, which suggests that it is a potent prognostic biomarker.

DNA methylation associated with etiological factors. A strong etiological factor in GC is *H. pylori*. Maekita *et al* (25) identified an association between *H. pylori* infection and hypermethylation of certain specific CpG islands. Furthermore, Chan *et al* (26) demonstrated that aberrant methylation of CpG islands in the epithelial cadherin promotor was an early event in *H. pylori*-induced GC carcinogenesis. Aberrant methylation has also been associated with Epstein-Barr virus, another virus associated with development of GC (27). Although associations between DNA methylation and habits including smoking or high sodium intake remain unclear, Xu *et al* (28) recently demonstrated that methylation of the gene encoding transmembrane protein 106A in primary GC was significantly associated with smoking and tumor metastasis. Furthermore, methylation of the genes encoding human MutL homolog 1 and human MutS homolog 3 were identified to be age-related and may therefore serve an important role in carcinogenesis of GC in the older population (29).

3. Histone modulation

Histone octamers package and order the DNA of eukaryotic cells into nucleosomes as part of the chromatin structure. Histones possess a tail-like structure that extends beyond the nucleosome and may be modulated; the majority of well-investigated histone modulations affect transcription. Histone modification assists with the regulation of pre-mRNA splicing (30). Ubiquitin-like containing PHD and RING finger domains 1-dependent histone H3 ubiquitination has been demonstrated to be critical in maintaining methylation during DNA duplication (31). Histone modulation, including methylation, acetylation, phosphorylation and ubiquitination, affect oncogene expression (32-36), although their clinical significance in patients with GC remains unclear. Cai *et al* (37) recently revealed that expression of histone-lysine N-methyltransferase *Suv39H1* and trimethylated histone H3 methylated lysine 9 (*H3K9*) was increased in GC, and trimethylated *H3K9* was identified to be positively associated with tumor stage and metastatic status (37).

4. Non-coding RNA

The Human Genome Project identified that although ~80% of the human genome is transcribed into RNA, only ~2% of those transcripts are translated into proteins. Numerous RNAs do not code for proteins in human cells, and are therefore called non-coding RNA. The functions of non-coding RNA have been partly elucidated, particularly for smaller transcripts. However, larger sized non-coding RNA is becoming more widely studied, particularly with regard to its roles in carcinogenesis and tumor progression.

MicroRNA (miRNA/miR). miRNA is a relatively short non-coding RNA of between 20 and 28 base pairs, and is derived from host DNA. miRNA has emerged as an important modulator of post-transcriptional regulation. miRNA regulates gene expression primarily by interfering with the transcription and cleavage of mRNA (38,39). This interference may explain some discrepancies between mRNA production and corresponding protein expression. miRNA targets are thought to include <30% of the human genome (40), and misregulation of miRNA expression affects development and progression of various diseases, including neoplasms. miRNA expression levels are widely reported to be associated with clinical effects of GC (41-68) (Table II). miRNA polymorphisms are also associated with GC outcomes. Stenholm *et al* (69) identified that polymorphisms of miR-26a, pre-miRNA of miR-27-a1 and pre-miRNA of miR-196-a2 were significantly associated with overall survival rates. As miRNA in formalin-fixed tissues is highly stable, and detection of circulating serum miRNA from tumors is widely studied, miRNA may be the basis of a novel system of detecting early-stage cancers (70). miRNA in serum is encapsulated in an 'exosome' that makes miRNA stable against various stresses and allows miRNA to be transferred between cells (71). Certain studies have investigated the possibility of using circulating miRNA as less invasive markers to detect and monitor GC (70,72,73).

Long non-coding RNA (lncRNA). Non-coding RNA transcripts of >200 base pairs are designated lncRNA. Previously, lncRNA was thought to be 'junk nucleotides', but recent evidence indicates that lncRNA is as important in epigenetic modulation as miRNA (74). Aberrant expression of certain types of lncRNA has been associated with poorer prognosis

Table I. Genes identified to exhibit an association with promoter methylation and clinical outcome.

Author, year	Gene	Function	Clinical association	(Refs.)
Graziano *et al*, 2004	CDH1	Regulates cell-cell adhesion, mobility and proliferation of epithelial cells	Poorer DFS, OS	(13)
de Maat *et al*, 2007	COX-2	Catalyzes prostaglandin production	Improved survival, time to recurrence	(14)
Ooki *et al*, 2010	HOPX-β	Cardiac growth and development	Poorer survival	(15)
Xu *et al*, 2012	BCL6B	Early B cell development	Poorer survival	(16)
Li *et al*, 2012	PAX5	B cell differentiation, neural development and spermatogenesis	Poorer survival	(17)
Du *et al*, 2012	ADAMTS9	Cleaves the proteoglycans aggrecan and versican	Poorer survival	(18)
Wang *et al*, 2013	ZNF545 (ZFP82)	Transcriptional regulation	Poorer survival	(19)
Guo *et al*, 2013	RKIP (PEBP1)	Involved in the presynaptic cholinergic neurons of the central nervous system	Poorer survival	(20)

CDH1, cadherin 1; DFS, disease-free survival; OS, overall survival; COX-2, cyclo-oxygenase 2; HOPX-β, HOP homeobox β; BCL6B, B cell CLL/lymphoma 6B; PAX5, paired box 5; ADAMTS9, a disintegrin and metalloproteinase with thrombospondin motifs 9; ZNF545, zinc finger 545; ZFP82, zinc finger protein 82; RKIP, Raf kinase inhibitor protein; PEBP1, phosphatidylethanolamine-binding protein 1.

Table II. miRNAs identified to be associated with clinical outcome of gastric cancer.

Author, year	miRNA	(Refs.)
Highly expressed		
Wang *et al*, 2013	miR-10b	(43)
Katada *et al*, 2009	miR-20b	(53)
Katada *et al*, 2009	miR-27a	(53)
Osawa *et al*, 2011	miR-34a	(65)
Inoue *et al*, 2012	miR-107	(42)
Liu *et al*, 2014	miR-132	(46)
Naito *et al*, 2014	miR-143	(49)
Katada *et al*, 2009	miR-150	(53)
Chen *et al*, 2013	miR-181a-5p	(54)
Brenner *et al*, 2011	miR-199a-3p	(56)
Yang *et al*, 2013	miR-214	(58)
Liu *et al*, 2012	miR-221	(61)
Wang *et al*, 2013	miR-301a	(62)
Yan *et al*, 2013	miR-335	(63)
Poorly expressed		
Liu *et al*, 2012	Let-7i	(41)
Wang *et al*, 2013	miR-22	(60)
Hashiguchi *et al*, 2012	miR-125a-3p	(44)
Guo *et al*, 2013	miR-127	(45)
Shin *et al*, 2013	miR-135a	(47)
Bao *et al*, 2011	miR-139	(48)
Akiyoshi *et al*, 2012	miR-144	(50)
Zheng *et al*, 2011; Sakamoto *et al*, 2014	miR-148a	(51,52)
Tan *et al*, 2014	miR-185	(55)
Tang *et al*, 2013	miR-200b	(57)
Tang *et al*, 2013	miR-200c	(57)
Wang *et al*, 2014	miR-214	(59)
Zheng *et al*, 2012	miR-409-3p	(64)
Guo *et al*, 2013	miR-433	(45)
Bandres *et al*, 2009	miR-451	(66)
Iwaya *et al*, 2013	miR-494	(67)
He *et al*, 2014	miR-760	(68)

miRNA/miR, microRNA.

in breast cancer (75), hepatocellular carcinoma (76) and lung carcinoma (77); and it has recently been demonstrated to possess clinical significance in GC (78-85) (Table III). lncRNA in plasma is reportedly detectable in patients with GC, as with miRNA (86).

5. Conclusions

In the present review, recent studies that have identified associations between epigenetic modulation and clinical outcomes in GC have been summarized and discussed. Epigenetic changes in the expression of specific genes critically affect their clinical significance. Further study may reveal epigenetic

Table III. Long non-coding RNA identified to be associated with promoter methylation and clinical outcomes.

Author, year	Gene	Status	Function	(Refs.)
Yang *et al*, 2012	H19	Increased	Cellular proliferation, p53 inactivation	(78)
Xu *et al*, 2013	HOTAIR	Increased	Poor OS, invasiveness	(79)
Yang *et al*, 2014	GHET1	Increased	Tumor size, tumor invasion and poor survival	(80)
Lee *et al*, 2014	nc886	Decreased	Poor survival	(81)
Xu *et al*, 2014	FENDRR	Decreased	Tumor invasion, stage, lymph node metastasis, poor prognosis	(82)
Han *et al*, 2014	LEIGC	Decreased	Tumor growth, cell proliferation, 5-FU sensitivity	(83)
Okugawa *et al*, 2014	MALAT1	Increased	Peritoneal dissemination	(84)
Xu *et al*, 2014	LSINCT5	Increased	Tumor size, depth, stage, worse DFS and DSS	(85)

H19, H19 imprinted maternally expressed transcript; HOTAIR, HOX transcript antisense RNA; OS, overall survival; GHET1, gastric carcinoma proliferation enhancing transcript 1; nc886, vault RNA 2; FENDRR, FOXF1 adjacent non-coding developmental regulatory RNA; LEIGC, lower expression in gastric cancer; 5-FU, 5-fluorouracil; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; LSINCT5, long stress-induced non-coding transcript 5; DFS, disease-free survival; DSS, disease-specific survival.

changes as the basis for targeted molecular therapy or novel biomarkers that predict GC prognosis or extension of this often fatal disease.

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