World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i38.13804

World J Gastroenterol 2014 October 14; 20(38): 13804-13819
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

Pathogenetic mechanisms in gastric cancer

Jing Shi, Yi-Ping Qu, Peng Hou

Jing Shi, Yi-Ping Qu, Peng Hou, Department of Endocrinology, The First Affiliated Hospital of Xi'an Jiaotong University School of Medicine, Xi'an 710061, Shaanxi Province, China
Author contributions: Shi J and Qu YQ collected and analyzed the literature; Hou P wrote the manuscript.
Supported by National Key Program for Developing Basic Research, No. 2010CB933903; the National Natural Science Foundation of China, No. 81171969, No. 81272933 and No. 81372217; and the Fundamental Research Funds for the Central Universities
Correspondence to: Peng Hou, PhD, Department of Endocrinology, The First Affiliated Hospital of Xi'an Jiaotong University School of Medicine, No. 277 of Yanta West Road, Xi'an 710061, Shaanxi Province, China. phou@mail.xjtu.edu.cn
Telephone: +86-298-5324039 Fax: +86-298-5324039
Received: October 24, 2013 Revised: April 30, 2014
Accepted: May 28, 2014
Published online: October 14, 2014

Abstract

Gastric cancer (GC) is a major public health issue as the fourth most common cancer and the second leading cause of cancer-related death. Recent advances have improved our understanding of its molecular pathogenesis, as best exemplified by elucidating the fundamental role of several major signaling pathways and related molecular derangements. Central to these mechanisms are the genetic and epigenetic alterations in these signaling pathways, such as gene mutations, copy number variants, aberrant gene methylation and histone modification, nucleosome positioning, and microRNAs. Some of these genetic/epigenetic alterations represent effective diagnostic and prognostic biomarkers and therapeutic targets for GC. This information has now opened unprecedented opportunities for better understanding of the molecular mechanisms of gastric carcinogenesis and the development of novel therapeutic strategies for this cancer. The pathogenetic mechanisms of GC are the focus of this review.

Key words: Gastric cancer; Risk factors; Genetic alterations; Epigenetic alterations; Signaling pathways

Core tip: Gastric cancer (GC) is a complex, multistep process involving environmental factors and deregulation of canonical oncogenic pathways. Central to these mechanisms are the genetic and epigenetic alterations in these oncogenic signaling pathways. We discuss the recent remarkable progress in understanding the molecular mechanisms and the opening of unprecedented opportunities for the development of novel therapeutic strategies for GC.

Shi J, Qu YP, Hou P. Pathogenetic mechanisms in gastric cancer. *World J Gastroenterol* 2014; 20(38): 13804-13819 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i38/13804.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i38.13804

INTRODUCTION

Gastric cancer (GC) is one of the most common cancers in the world, particularly in developing countries, and the mortality of GC is the second leading cause of cancer-related deaths[1-3]. It is often not detected until an advanced stage; consequently, the 5-year survival rate is low (10%-20%)[4]. About 95% of gastric tumors are adenocarcinomas, which can be classified into well-differentiated (intestinal), undifferentiated (diffuse), and 'mixed' types[5]. Although the incidence is declining, its prognosis remains poor. Epidemiological evidence indicates that environmental factors play a major role in the carcinogenesis. Among the environmental factors, diet and infection with *Helicobacter pylori* (*H. pylori*) are the most common suspects in gastric tumorigenesis[6,7]. In addition to environmental factors, GC is a complex, multistep process involving deregulation of canonical oncogenic pathways. These oncogenic signaling pathways can be overactivated by some genetic and epigenetic alterations[8,9]. Genetic alterations,

such as gene mutations, gene amplification, deletions or allelic loss and chromosomal translocations, can cause gain-of-function in oncogenes and loss-of-function in tumor suppressor genes, ultimately contributing to gastric carcinogenesis[9,10]. Moreover, like other human cancers, gastric tumorigenesis can also be profoundly influenced by epigenetic abnormalities, such as aberrant gene methylation, histone modification and microRNAs[10,11]. For example, promoter hypermethylation as an important hallmark of cancer cells is one of the major mechanisms to inactivate tumor suppressor genes in gastric tumorigenesis[11,12]. Increasing evidence indicates that most cancer phenotypes are largely governed by complex interactions between multiple pro- and anti-oncogenic signaling circuits[13]. This review discusses the recent remarkable progress in understanding the molecular pathogenesis and mechanisms of GC.

ENVIRONMENTAL RISK FACTORS

GC, like other cancers, is the end result of the interplay of many risk factors as well as protective factors. Environmental and genetic factors are also likely to play a role in the etiology of this disease. Among the environmental factors, it is clear that *H. pylori* infection and diet are strong and established risk factors of GC[6,7].

H. pylori infection is an important and established risk factor of GC. About 50% of the world's population are infected by *H. pylori*; most of the infected individuals remain asymptomatic and fewer than 0.5% of infected individuals will develop GC. Although *H. pylori* infection is thus not a sufficient cause for the development of GC[14], *H. pylori* infection has been associated with high prevalence of GC and can also be found in the gastric mucosa of patients with chronic gastric inflammation[15,16]. The connection between *H. pylori* and GC is not only based on epidemiologic data and animal models[17-19], but data from clinical trials have also suggested that *H. pylori* eradication therapy can effectively reduce the development of precancerous lesions and GC[20]. *H. pylori* infection causes chronic inflammation, accumulation of reactive oxygen species (ROS) and oxidative DNA damage in the gastric mucosa, and promotes the sequential progression of normal gastric epithelium through atrophic gastritis, intestinal metaplasia, and dysplasia to carcinoma[21]. Intestinal metaplasia is a preneoplastic lesion and confers increased risk for GC development. However, the molecular networks connecting infection to lesion formation and the cellular origin of this lesion remain largely unknown[22]. Although the intestinal-type GC are more related to atrophic gastritis, intestinal metaplasia and dysplasia, *H. pylori* infection also can increase the risk of diffuse-type GC. Moreover, *H. pylori* infection enhances aberrant promoter methylation in gastric mucosa, contributing to gastric tumorigenesis by silencing tumor suppressor genes[23-25]. However, *H. pylori* infection cannot affect mRNA and protein expression of DNA methyltransferases (DNMTs)[23,26]. Until now, the molecular mechanism of *H. pylori*-induced aberrant gene methylation in GC remains poorly understood.

In addition to *H. pylori* infection, dietary and lifestyle factors also increase the risk of gastric carcinogenesis. An excessive intake of starch, fat, meat, salt and N-nitroso compounds poor in protein quality increases the risk of GC, especially preserved food rich in salt, salt *per se* and N-nitroso compounds; whereas a diet rich in fresh fruits, vegetables and dietary fiber can decrease the risk of GC[14,27]. N-methyl-N-nitro-N-nitrosoguanidine (MNNG) is one of the known gastric carcinogens, which enhance the carcinogenic effects[28,29]. N-nitroso compounds can be formed by the reaction of nitrate or nitrite during the process of preservation and during digestion in the stomach, and they may be present in some foods including cured meats, dried milk, instant soups, and coffee dried on direct flame[30-32]. Ingestion of salt-preserved food can induce direct damage to the gastric mucosa resulting in gastritis and can increase the risk of persistent *H. pylori* infection; examples are salted fish, soy sauce, pickled vegetables, cured meat[33,34]. Moreover, high starch and low protein diets may favor acid-catalyzed nitrosation in the stomach and cause mechanical damage to the gastric mucosa[14,35]. Fruits and vegetables are rich sources of carotenoids, vitamin C, folate and phytochemicals, and may modestly reduce risk in the process of carcinogenesis[14,34,35]. It has been reported that epigallocatechin gallate (EGCG) is the most abundant polyphenol in green tea and it possesses a significant protective effect against *H. pylori*-induced cytotoxicity in gastric epithelial cells[36].

Other established lifestyle factors, including cigarette smoking and alcohol consumption, may affect the risk of GC[37,38]. Alcohol, a gastric irritant, is an important risk factor for GC. Tobacco has been reported to induce the development of precursor gastric lesions and increase the incidence of *H. pylori* infection. Accumulated evidence has shown an association between gastroesophageal reflux disease (GE reflux) and elevated risk for diffuse-type GC[39-41]. In addition, Epstein-Barr virus (EBV) infection is also closely associated with gastric carcinogenesis[38].

ALTERED SIGNALING PATHWAYS IN GC

GC is a complex and molecularly heterogeneous disease involving deregulation of canonical oncogenic pathways, such as p53[42], wnt/β-catenin[43], nuclear factor (NF)-κB[44] and PI3K/Akt[45] pathways. Central to these mechanisms are the genetic and epigenetic alterations in these oncogenic signaling pathways[8,9]. Of them, some molecular alterations are closely associated with poor clinical outcomes of GC patients and are summarized in Tables 1 and 2.

p53 pathway

Gene mutations play a key role in transforming normal cells into cancerous cells; they directly or indirectly suppress the normal function of tumor suppressor genes, or enhance transforming activity of oncogenes. So far, numerous gene mutations have been identified in GCs.

One of the most commonly mutated genes is *TP53* in GC, which encodes p53 protein[46]. Tumor suppressor p53 plays a fundamental role in the regulation of the cell cycle and apoptosis, and its inactivation is central to the pathogenesis of many human cancers, including GC[46]. Numerous reports have demonstrated that the function of *TP53* is more frequently inactivated in GCs by mutations and loss of heterozygosity (LOH) than by DNA methylation. *TP53* mutation pattern is characterized by frequent G:C→A:T mutations at CpG sites. There are about 30%-70% of GCs containing *TP53* point mutations. *TP53* mutations are an early event in GC and show a different pattern in diffuse- or intestinal-type GC. Mutations of *TP53* seem to be an early event and not related to tumor stage in intestinal-type GC, but their frequency increases with stage progression and they are common in diffuse-type GC[42,46-48]. It has been reported that there is significant correlation between LOH of *TP53* with gastric precancerous lesions, suggesting that loss of *TP53* may be an early event in gastric carcinogenesis[49]. Cyclin-dependent kinase (CDK) inhibitor *p21* gene is directly involved in human carcinogenesis through directly inhibiting DNA replication[50]. It has been reported that the expression of *p21* is usually assessed in combination with *TP53* status, and GC patients with loss of *p21* have worse survival[51]. Thus, aberrant p53 pathway may play an important role in gastric carcinogenesis.

PI3 kinase/Akt pathway

The PI3 kinase (PI3K)/Akt signaling pathway regulates cellular metabolism and growth by acting as a cellular sensor for nutrients and growth factors and plays an important role in tumorigenesis[52-54]. PI3K is a lipid kinase, which is mainly activated by tyrosine kinases. PIK3CA is a catalytic 110-kDa subunit of PI3 kinase and an activator of the PI3K/Akt pathway. It is frequently activated by genomic amplification[55] or mutation[56-58]. Gene amplification is one of the most frequent genomic alterations found in human cancers[59-62]. Increased gene dosage by this genetic event is a common mechanism for oncogene overexpression during tumorigenesis[63], and also reflects the genetic instability of the tumor cells like other types of genetic alterations[64]. Our recent study has demonstrated that *PIK3CA* mutations are not common, but its amplification is very common in GC[55]. Notably, *PIK3CA* amplification is associated with elevated p-Akt, suggesting that this genetic alteration may be a major mechanism in activating the PI3K/Akt signaling pathway, further contributing to gastric tumorigenesis[55].

PTEN encodes a multifunctional phosphatase that negatively regulates cell growth, migration and survival *via* the PI3K/Akt signaling pathway. Mutations, LOH and promoter methylation in the *PTEN* gene have been frequently identified in GC[48,65,66]. These genetic/epigenetic alterations ultimately contribute to overactivation of the PI3K/Akt signaling pathway during gastric tumorigenesis.

ERBB3 is a member of the epidermal growth factor receptor (EGFR) family or ERBB tyrosine kinase (TK) receptor family, and plays important roles in animal development; deregulation has been linked to several pathologies, including cancer. This receptor family mediates cell proliferation and survival by the MAPK and PI3K/Akt signaling pathways[67]. *ERBB3* overexpression is frequently found in GC, particularly in the diffuse-type tumors, contributing to the overactivation of the PI3K/Akt pathway[68]. Thus, aberrations of the ErbB3/PI3 kinase pathway may play an important role in diffuse-type GC. Collectively, specific genotype-based targeting against the PI3K/Akt signaling pathway may be an effective therapeutic strategy for GC.

MAPK pathway

The MAPK (Ras/Raf/Mek/Erk) signaling pathway regulates a series of cell activities such as angiogenesis, proliferation, differentiation, apoptosis and migration. The MAPK pathway consists of several kinases, including Ras, Raf, and Mek, and is often deregulated in GC[69]. Ras (H-, K-, N-isotypes), which encode small G proteins, belong to a commonly mutated oncogene family and function as molecular switches of numerous signaling cascades, including MAPK pathway[70]. Mutations of *KRAS* and *BRAF* are common in GC[71-73]. *ERK1/2*, the final effectors of this pathway, are also found to be activated in GC[74]. In addition, tumor suppressor gene *RASSF1A* (ras-association domain family 1A), *RASSF2*, and *HRASLS* are usually silenced by promoter hypermethylation in various human cancers, including GC[12,75-78]. Especially, *RASSF1A* contains a ras-association (RA) and a Sav/RASSF/Hpo (SARAH) domain. Its inactivation by promoter methylation can activate the MAPK signaling pathway, and effectively block cancer cell apoptosis, ultimately contributing to tumorigenesis, including GC[48,79].

EGFR is a member of the EGFR family, and works as a cell surface receptor of extracellular ligands, including epidermal growth factor (EGF) and transforming growth factor alpha. Ligand binding to EGFR extracellular domain leads to the phosphorylation of its intracellular tyrosine kinase domain. This will initiate a series of intracellular signals, such as activation of the MAPK signaling pathway[80]. *EGFR* overexpression is frequently found in GC and is associated with the depth of invasion and poor survival of GC patients[81]. ERBB2, a member of the EGFR family, does not have any specific ligands that it binds directly and may be regulated by ligands in the same way as EGFR. Amplification or overexpression of *ERBB2* is very common in intestinal-type GC, but not in diffuse-type GC[68,82,83]. Activated ERBB2 oncogenic pathway may play an important role in intestinal-type GC. *ERBB2* mutations occasionally occur in metastatic gastric carcinoma, suggesting that these mutations play a role in the metastatic process of some GCs[82]. However, as compared with mutations, overexpression of *ERBB2* caused by copy number gain is more commonly found in human cancers, including GC[84]. Strikingly, *ERBB2* amplification may serve as a prognostic marker for tu-

mor invasion, lymph node metastasis and poor prognosis[68,83,85]. Our recent study has demonstrated frequent *ERBB4* amplification in GC and is strongly associated with poor survival of GC patients[86]. In addition, MiR-125a-5p, which targets *ERBB2*[87], and miR-146a, which targets both *EGFR* and *IRAK1*[88], are related to survival and may be prognostic factors in GC.

Taken together, these findings suggest that the MAPK pathway plays an important role in gastric tumorigenesis, and may be an effective therapeutic target for GC.

Wnt pathway

Wnt signaling regulates several biological processes, such as determination of cell fate, morphology, polarity, adhesion and growth[89,90] and is divided into canonical and non-canonical pathways. In the former, wnt signals stabilize β-catenin (or *CTNNB1*), hereby activating gene transcription through interaction of β-catenin with transcriptional factors[89]. Numerous reports have demonstrated that this pathway plays an important role in the invasion and metastasis of GC and may be a good indicator for evaluating the biological behavior of GC[91,92]. The non-canonical pathway is not related to β-catenin and is involved in embryonic development and cell polarity, as well as being also linked to the development of GC[93,94].

APC (adenomatous polyposis coli) is involved in chromosomal segregation, and its inactivation causes aneuploidy and perturbed structure of the chromosomes[95,96]. *β-catenin* mutations or *APC* inactivation can cause accumulation and high intranuclear levels of β-catenin, which regulate the wnt signaling pathway and play an important role in early tumor growth, including GC[10,48]. Mutation of the *β-catenin* gene may function in initiation of invasive processes in intestinal-type GC[97]. The *APC* gene product binds to the multifunctional protein β-catenin, whose free concentration within the cell is strictly regulated and kept at a low level. Inactivation of the *APC* gene is more frequently caused by mutations and LOH than DNA methylation. *APC* mutations are frequently associated with moderately well differentiated intestinal-type tumors[98,99]. There are about 30%-40% of GCs that show LOH in the *APC* gene[48]. E-cadherin, a calcium dependent cell-to-cell adhesion glycoprotein, is encoded by the *CDH1* gene and plays a critical role in maintaining the normal epithelium architecture[100]. The cytoplasmic domain of this molecule interacts with β-catenin, forming strong cohesive nets between the actin cytoskeleton[101], essential for processes of cell-cell adhesion and cell shape, polarity, migration and invasion. Inactivation of *CDH1* induced by mutation, LOH or aberrant promoter methylation markedly reduces cell adhesion, alters morphology and enhances cellular motility[10,11,48,102], resulting in tumor dedifferentiation, invasiveness, metastasis and prognosis[103-105]. It has been reported that approximately 50% of diffuse GC is associated with loss of *CDH1* function caused by mutations, LOH and promoter methylation[105,106].

In addition, several antagonists of wnt signaling have been identified with two functional classes: the secreted frizzled-related protein (sFRP) class and the dickkopf (Dkk) class[107]. Recent studies on GC have described aberrant methylation for several regulators of the wnt pathway, including *SFRP1*, *SFRP2*, *SFRP4*, *SFRP5*, *Dkk-3* genes[107-109], further implicating the role of the wnt pathway in gastric tumorigenesis.

NF-κB pathway

NF-κB is a critical regulator of genes involved in cell survival and proliferation, cellular stress response and inflammation[110,111]. It is well documented that chronic infections and inflammation serve as major risk factors for various types of cancer, including GC[9]. NF-κB can activate the genes in response to certain stimuli, including ROS, tumor necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β), and bacterial lipopolysaccharides (LPS)[112]. Activation of NF-κB is by the canonical/classical and non-canonical/alternative pathways. The canonical pathway can be activated by several stimuli, such as inflammation cytokines and antigens[113]. The non-canonical pathway is induced by certain receptor signals like B-cell activating factor (BAFF), lymphotoxin β (LTβ), CD40 ligand, TNF-like weak inducer of apoptosis (TWEAK) and receptor activator of NF-κB ligand (RANKL)[114]. There is evidence that NF-κB is constitutively activated in GC tissues, with high levels in GC cell lines as compared with normal adjacent epithelial cells[115]. More importantly, GC patients with high NF-κB levels in cancer cells have a lower survival time than those with low NF-κB activation[116].

Transforming growth factor-β signaling

Transforming growth factor beta (TGF-β) is a multifunctional cytokine that controls differentiation, apoptosis, cell growth and immune reactions. The TGF-β family mainly includes three isoforms, TGF-β1, TGF-β2, TGF-β3, in mammals[117,118]. In early stages of GC, TGF-β signaling is considered to be a tumor suppressor pathway, whereas in the late stage it promotes invasion and metastasis[119]. The TGF-β signaling pathway is composed of two distinct receptors with intrinsic serine/threonine kinase activity, TGF-β receptor type Ⅰ, type Ⅱ (TGFBR1 and TGFBR2) and Smad proteins. The loss of TGF-β response due to the dysregulation of *TGFBR1*, *TGFBR2* and *Smad4* is well known for its contribution to oncogenesis. Moreover, methylation of *TGFBR1*, *TGFBR2* and *Smad4* may exist in the gastric cardia dysplasia stages and plays a key role in these genes silencing with subsequent effects on the TGF-β/Smad signaling pathway[120]. TGF-β induces *RUNX3*, a transcription factor that is an inhibitor of the wnt signaling pathway and has been involved in gastric tumorigenesis. Reduced expression of *RUNX3* in GC has been attributed to aberrant promoter methylation. In addition, MiR-130b is identified as the top candidate miRNA for RUNX3 binding. Its overexpression can downregulate *RUNX3* expression[121]. Importantly, loss of *RUNX3* expression is closely associ-

ated with the progression, differentiation, metastasis and poor prognosis of GC[122-124].

Cyclooxygenase -2/Prostaglandin E2 pathway

Cyclooxygenase-2 (COX-2) is a rate-limiting enzyme responsible for the conversion of arachidonic acid to prostaglandins (PGs)[125]. Its overexpression has been reported in various human cancers, including GC[126,127]. Moreover, several studies have shown that treatment with COX-2 selective inhibitors suppresses chemically induced tumor formation and xenografted tumor growth[128]. These findings suggest that the COX-2 pathway plays an essential role in GC development. COX-2 is responsible for catalyzing the biosynthesis of PG-H2, which is further converted to prostaglandin E2 (PGE2) by microsomal PGE synthase-1 (mPGES-1)[129]. COX-2-derived PGE2 can promote cell growth, inhibit apoptosis and enhance cellular invasiveness, facilitating cancer progression[130]. Up-regulation of PGE2 is found in most of the gastrointestinal cancers[131], indicating that an increased level of PGE2 through induction of COX-2 and mPGES-1 is crucial for gastric tumorigenesis.

Retinoblastoma pathway

The retinoblastoma (Rb) family is involved in cell cycle regulation and their function and/or expression is often lost in various kinds of tumors[132]. In normal cells, the cell cycle is controlled by a complex series of signaling pathways by which a cell grows, replicates its DNA and divides. Dysregulation of cell cycle components can cause tumor formation[133]. Tumor suppressor gene *p16* is a CDK inhibitor that slows down the progression of the cell cycle by inactivating the cyclin dependent kinase that phosphorylates Rb protein[134,135]. Thus, *p16* contributes to the maintenance of Rb in an unphosphorylated state and inhibits cell cycle progression. Mutations in *p16* gene are frequently found in human cancers, including GC[10,48,136]. Our previous studies have shown that there is close association of hypermethylation of *p16* with poor survival of GC patients[12,75] and methylation status of *p16* can predict response to 5-FU[137]. Strikingly, *p16* methylation can be detected in 19%-51.9% and 25%-57.4% of serum extracted from GC patients[138,139], implicating its significance in the diagnosis and prognosis of GC.

Others

Many other molecular events are also found in gastric carcinogenesis (Tables 1 and 2). For example, the majority of GC is characterized by genetic instability, which is generally classified into two major types: microsatellite instability (MSI) and chromosomal instability (CIN)[140,141]. MSI is characteristic for the hereditary type of GC and results from errors in DNA replication. These replication errors are detected and repaired by a complex of mismatch repair (MMR) proteins[140], including hMLH1 and hMSH2. Functional inactivation of MMR can be caused by gene mutations and CpG island methylation. Inactivation or deficiency of MMR genes often leads to inactivation of tumor suppressor genes, LOH and mutations in critical genes. CIN is characterized by gross chromosomal abnormalities[141], resulting in major modifications of chromosomal quantity or quality, including genomic amplifications of oncogenes and/or LOH, deletions or allelic loss, chromosomal translocations. Of them, chromosomal translocations lead to the formation of protein coding genes with oncogenic functions and rearrangements of chromosomes. A recent study has shown that *CD44-SLC1A2* gene fusions are detected in 1% to 2% of GCs, but not in adjacent matched normal gastric tissues. Fusion of the *SLC1A2* gene coding region to *CD44* regulatory elements likely causes *SLC1A2* transcriptional dysregulation[142]. Thus, the genomics of GC display high instability and all these abnormalities may lead to oncogene activation and/or tumor suppressor gene inactivation.

In addition to DNA methylation, microRNAs (miRNAs) and histone modifications are important epigenetic modifications, which play critical roles in gastric tumorigenesis[143-145]. MiRNAs can function as either tumor suppressors or oncogenes depending upon their target genes. Many tumor suppressor miRNAs that target growth-promoting genes are downregulated in human cancers, whereas oncogenic miRNAs that target growth inhibitory pathways are often upregulated in cancer cells[146]. For example, miR-9 and miR-433, which target tumor-associated genes *GRB2* and *RAB34* respectively, are significantly down-regulated in GC as compared with adjacent normal tissues[147]. MiR-146a, which targets both *EGFR* and *IRAK1,* is related to survival and may be a prognostic factor in GC[88]. Histones are structural proteins of chromatin and are composed of five basic proteins: H1, H2A, H2B, H3 and H4. The N-terminal tails of histones are subject to posttranslational covalent modifications, including methylation, acetylation, ubiquitination, sumoylation, phosphorylation, proline isomerization and ADP ribosylation. These modifications can alter chromatin remodeling, and histone acetylation and methylation are associated with pathological epigenetic disruption in cancer cells[148,149]. High levels of H3K4me3 (trimethylation of lysine 4 on histone H3), H3K36me3, H3K79me3, H4K20me1, H3K27ac, H2BK5ac are associated with actively transcribed genes. In contrast, low levels of acetylation and high levels of methylation of H3K27, H3K9 and H4K20 are associated with transcriptional repression[144]. For example, H3K9me3 is positively correlated with tumor stage, lymphovascular invasion, tumor recurrence and poor survival, indicating that histone modification may be a useful predictor for poor prognosis of GC patients[150]. Collectively, these observations suggest that miRNAs and histone modification may play a key role in gastric carcinogenesis and are closely associated with worse prognosis of cancer patients.

TRANSLATIONAL PROMISES IN GC

GC is a complex disease that involves multiple risk factors and multiple genetic/epigenetic alterations. Cur-

Table 1 Genetic alterations in gastric cancer

Genes	Alterations	Function	Pathology	Prognosis	Ref.
Tumor suppressor genes					
TP53	Mutation/LOH	Transcription factor	Both	Association with poor survival	[42,46,48,182]
APC	Mutation/ LOH	Signal transduction	Intestinal	Association with poor survival	[48,98,99]
CDHI	Mutations/LOH	Adhesion	Diffuse	Association with poor survival	[48,102,106,183,184]
hMLH1/hMSH2	Mutations	DNA mismatch repair	Both	Association with poor survival and microsatellite instability	[10,140,185]
p16	Mutations/LOH	Cell cycle	Both	LOH of p16 association with lymph metastasis	[48,136,186,187]
RIZ	Mutations/LOH	Nuclear histone/protein methyltransferase	-	Association with microsatellite instability	[188-190]
hMSH3	Mutations	DNA mismatch repair	-	Association with microsatellite instability	[191,192]
hMSH6	Mutations	DNA mismatch repair	-	Association with microsatellite instability	[191,192]
PTEN	Mutations/LOH	protein tyrosine phosphatases	Both	Association with TNM stage, lymph node metastasis and poor survival	[65,66,193,194]
bcl-2	LOH	Apoptosis inhibitor	Intestinal	Association with invasion depth and lymph node metastasis	[182,195]
DCC	LOH	Cell adhesion	Intestinal	Association with poor survival	[48,196]
NM23	LOH	Nucleoside diphosphate kinase	Both	Association with metastasis and poor survival	[197-199]
p21	Loss	Cell cycle	Both	Association with poor survival	[51]
FHIT	LOH	Purine metabolism	Both	Association with invasive depth and microsatellite instability	[200]
BRCA1	LOH	Genetic instability	Both	Association with poor survival	[201,202]
Oncogenes					
β-*Catenin*	Mutations	Adhesion, Signal transduction	Intestinal	Association with poor survival and EBV-associated GC	[10,58,97]
BRAF	Mutations	Signal transduction	Both	Association with microsatellite instability	[71,203]
K-Ras	Mutations	Signal transduction	Intestinal	Association with poor prognosis and microsatellite instability	[57,71-73,204]
PIK3CA	Amplification Mutations	Signal transduction	Both	Association with poor survival	[55-58]
EGFR	Amplification	Growth factor receptor Tyrosine kinases	Both	Association with poor survival	[57,81,205]
ERBB2	Amplification	Growth factor Receptor	Intestinal	Association with poor survival	[68,81-85,205]
	Mutations	Tyrosine kinases			
ERBB3	Overexpression	Growth factor receptor Tyrosine kinases	Diffuse	Association with poor survival	[68,81,85]
ERBB4	Amplification	Growth factor receptor Tyrosine kinases	Both	Association with poor survival	[86]
c-Met	Amplification	Growth factor receptor	Diffuse	Association with poor survival	[86,206]
KSAM	Amplification	Growth factor receptor	Diffuse	Association with poor survival	[207]
VEGF	Overexpression	Growth factor	Intestinal	Association with metastasis and poor survival	[153,154,208]
CD44	Amplification	Cell adhesion	Both	Association with metastasis and poor survival	[86,209]
PRL3	Amplification	Cell signaling molecules	Both	Association with metastasis and poor survival	[210,211]
c-Myc	Amplification	Transcription factor	Intestinal	Association with poor survival	[212,213]
Cyclin E	Amplification	Cell cycle regulator	Both	Association with poor survival	[208,214]

LOH: Loss of heterozygosity.

rently, surgical resection and chemotherapy are important strategies for GC treatment. However, despite recent advances in perioperative and adjuvant chemotherapy, most patients with advanced GC still have a poor prognosis. Thus, a better understanding of the pathogenetic mechanisms of GC may lead to new diagnostic, therapeutic and preventive approaches to this disease. Screening and treatment of *H. pylori* infection, restriction of dietary salt, and a diet rich in fresh fruits and vegetables can decrease the risk of GC and prevent GC[20]. In addition, identification of genetic and epigenetic markers in GC patients may be an encouraging factor to advance individualized and targeted therapies.

In recent years, in the ToGA study, trastuzumab, which is a specific antibody for ERBB2, has been approved as a current standard of chemotherapy in ERBB2-positive GC patients[151,152]. Given that VEGF overexpression is often found in GC, and is related to tumor aggressiveness, VEGF may thus become a valid target for antiangiogenic therapy[153,154]. Anti-VEGF agents have recently been developed, including mAbs and TKIs (the tyrosine kinase inhibitors). Bevacizumab, the VEGF monoclonal antibody, is currently being investigated for GC treatment in combination with different

Table 2 Epigenetic alterations in gastric cancer

Genes	Function	Prognosis	Detected in serum	Ref.
DNA methylation				
BRCA1	DNA repair	Association with age	-	[215]
hMLH1	DNA repair	Association with poor survival	Yes	[75,216]
MGMT	DNA repair	Association with poor survival	-	[75]
RASSF1A	DNA repair/Cell cycle	Association with poor survival	Yes	[74,76,77]
CDH1	Cell invasion/Metastasis	Association with poor survival	Yes	[105,106,138,139,216,217]
RASSF2	DNA repair/Cell cycle	Association with poor survival	-	[75]
P16	Cell cycle	Association with poor survival	Yes	[75,137-139,218]
IGFBP3	Cell cycle	Association with lymph node metastasis	-	[219]
CHFR	Cell cycle	Association with invasion depth, differentiation and lymph node metastasis	-	[218,220]
P15	Cell cycle	-	Yes	[139,221]
ADAM23	Cell invasion/metastasis	-	-	[222,223]
APC	Cell invasion, Metastasis, Signal transduction	Association with poor survival	Yes	[216]
LOX	Cell invasion and metastasis	Association with Helicobacter pylori-positive individuals	-	[22]
TIMP3	Cell invasion and metastasis	Association with poor survival	Yes	[74,216]
HAND1	Cell differentiation	Association with poor survival	-	[22,75]
MLF1	Cell differentiation	Association with lymph node metastasis	-	[75,223]
PRDM5	Cell differentiation	-	-	[223,224]
RORA	Cell differentiation	-	-	[223]
NDRG2	Cell differentiation	Association with lymph node metastasis	-	[225]
BNIP3	Apoptosis	Association with poor survival	-	[226,227]
DAPK	Apoptosis	Association with poor survival	Yes	[74,139,218,227,228]
TMS	Apoptosis	Association with poor survival	-	[228]
FHIT	Apoptosis	Association with lymph node metastasis	-	[105]
GSTP1	Apoptosis	Association with EBV-related gastric cancer	Yes	[139,229]
FLNc	Cell morphology	Association with poor survival	-	[75]
RUNX3	Transcriptional factor, Signal transduction	Association with poor survival	Yes	[120,122,123,218,220]
ZNF545	Transcriptional factor	Association with poor survival	-	[230]
RARβ	Signal transduction	Association with poor survival	Yes	[74,138]
HRASLS	Signal transduction	-	-	[75]
SFRP2	Signal transduction	-	-	[108,231]
SFRP1	Signal transduction	Association with lymph node metastasis	-	[231]
MicroRNAs				
let-7g	Tumor suppressor	Association with invasion depth, lymph node metastasis	-	[232]
miR-433	Tumor suppressor	Association with invasion depth, lymph node metastasis	GRB2	[147,232]
miR-1	Tumor suppressor	Association with tumor stage	-	[233]
miR-20a	Tumor suppressor	Association with tumor stage	-	[233]
miR-27a	Tumor suppressor	Association with tumor stage	-	[233]
miR-34	Tumor suppressor	Association with tumor stage	Bcl-2, Notch, and HMGA2	[233,234]
miR-423-5p	Tumor suppressor	Association with tumor stage	-	[233]
miR-125a-5p	Tumor suppressor	Association with tumor size, invasion, liver metastasis, and poor survival	ERBB2	[87]
miR-146a	Tumor suppressor	Association with lymph node metastasis, venous invasion, and poor survival	EGFR, IRAK1	[87]
miR-9	Tumor suppressor	-	RAB34, CDX2, and NF-κB1	[147,234,235]
miR-375	Tumor suppressor	-	PDK1, 14-3-3zeta	[236]
miR-433	Tumor suppressor	-	GRB2	[147]
miR-214	Oncogenesis	Association with invasion depth and lymph node metastasis	-	[232]
miR-130b	Oncogenesis	-	RUNX3	[121]

chemotherapeutic compounds in a phase Ⅲ (AVAGAST) study. Strikingly, adding bevacizumab to chemotherapy is associated with significant increases in PFS (progression-free survival) and overall response rate in the first-line treatment of advanced GC[155]. Apatinib, a TKI that selectively targets VEGFR-2 (a type Ⅲ receptor tyrosine kinase), has been investigated in a phase Ⅱ clinical trial that shows that apatinib improved PFS and OS (overall survival) in heavily pretreated patients with metastatic GC[156]. Other anti-VEGF agents, such as ramucirumab, sunitinib, sorafenib and cediranib, have also been investigated for GC treatment[157].

Specific inhibitors against molecular target EGFR have been developed in GC treatment although not com-

pletely effective and they need further investigation. Anti-EGFR mAbs and TKIs are currently undergoing clinical trials for GC patients. Cetuximab has shown some encouraging results when combined with other chemotherapeutic agents in phase Ⅱ trials, whereas the phase Ⅲ trial (EXPAND) demonstrates that addition of cetuximab to capecitabine-cisplatin provided no additional benefit to chemotherapy alone in the first-line treatment of advanced GC[158]. Lapatinib, a TKI, inhibits both EGFR and ERBB2 kinases. Although a poor objective response rate has been observed in the phase Ⅱ studies[159,160], phase Ⅲ studies are evaluating the role of lapatinib in conjunction with chemotherapy[161]. Compounds against other novel targets, such as mechanistic target of rapamycin mTOR (everolimus)[162,163], hepatocyte growth factor receptor c-Met (foretinib[163] and rilotumumab[152]), KSAM (AZD4547)[152], MMP (marimastat)[164], and protein kinase C (bryostatin-1)[165], have also been investigated in GC.

Epigenetic changes in DNA are reversible, different from genetic changes, and they represent very attractive targets for new therapeutic approaches. Several epigenetic drugs targeting DNA methylation and histone deacetylation enzymes have been investigated in clinical trials. Treatments targeting cancer are designed to inhibit either the function of DNMTs or histone deacetylase (HDAC). DNMT inhibitors are divided into two families: the nucleoside analogs and the non-nucleoside inhibitors. The three most commonly used catalytic inhibitors of DNMTs are the nucleoside analogs 5-azacytidine, 5-aza-2-deoxycytidine, and zebularine. The first DNA methylation inhibitor 5-azacytidine (azacitidine) and 5-aza-2-deoxycytidine (decitabine) have been recently approved by the FDA for treatment of myelodysplastic syndromes (MDS) and primary cutaneous T-cell lymphoma (CTCL)[166-168]. However, 5-azacytidine and 5-aza-2-deoxycytidine have a weak response in solid tumors[169]. SGI-110, a second generation DNMT inhibitor, is being investigated in phase Ⅱ clinical trials for the treatment of MDS and acute myeloid leukemia(AML)[170,171]. Zebularine and 5-azacytidine need to be incorporated into DNA to trap DNMTs; they may have additional nonspecific toxicities, whereas non-nucleoside molecules, such as EGCG and genistein, do not rely on DNA incorporation. EGCG, the main polyphenol of green tea, and genistein have been characterized as enzymatic and cellular DNMT inhibitors[172,173]. Other commonly used drugs have been shown to bring about DNA demethylation, such as procainamide and hydralazine[174]. HDAC inhibitors (HDACis) now also are considered as potential therapeutics. Trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA) are the classic HDACis. HDAC inhibitors can induce cell differentiation, apoptosis, and growth suppression and may be an innovative approach in GC treatment[175]. Vorinostat (SAHA), also known as suberoylanilide hydroxamic acid, is the first clinically approved HDACi, which has been recently approved for clinical use in CTCL[176]. Preclinical studies have shown that vorinostat has potential antitumor activity, including in GC, and may improve clinical outcomes for GC patients[177]. A phase I study of vorinostat combined with capecitabine and cisplatin has been performed to assess the recommended phase Ⅱ trial dose in patients with advanced GC[178]. These findings suggest that a new area of potential interest is the development of histone methyltransferase (HMTase) inhibitors. HMTase inhibitors may be used therapeutically to activate silenced tumor suppressor genes.

CONCLUSION

In addition to environmental factors, gastric carcinogenesis involves complex genetic and epigenetic alterations. It is now well established that genetic/epigenetic alterations can be driver events in the progression of normal gastric mucosa to cancer. Moreover, these alterations also contribute to the molecular heterogeneity of GC, as illustrated by the identification of molecular subtypes of GCs that can be identified by their unique genetic/epigenetic signatures. Given the role of these molecular events in directing the pathogenesis of GC, studying their signatures and developing them as biomarkers for diagnosis, prognosis and direction of therapy is likely to yield clinically useful assays that will be used to direct patient care.

In recent years, a large number of biomarkers have been developed for the early detection and prognostic evaluation of GC, as well as for predicting response to relevant therapies. However, in many important diagnostic scenarios, DNA from the cancer cells represents only a small fraction of the total DNA in the clinical sample, such as plasma, serum, urine, feces, or sputum. An exciting evolution of the development of biomarkers is the improvement of the biotechnology, such as next generation sequencing or deep sequencing, which now allows us to profile genetic/epigenetic alterations at a much higher sensitivity and genomic scale previously not possible[179,180].

Although recent diagnostic and therapeutic advances have provided excellent survival for patients with early GC, patients are usually diagnosed at an advanced stage and the prognosis is still dismal[181]. Thus, there is a pressing need to develop effective therapeutic strategies for this disease. Increasing evidence has demonstrated that combinations of various targeted agents with chemotherapies will be an effective strategy for GC treatment. In addition, continued efforts to investigate these molecular events will allow for a better understanding of the pathogenesis of GC and will lead to the translation of these insights into the clinical arena.

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P- Reviewer: Beltran MA, Caboclo JLF, Fassan M, Ierardi E, Kakushima N, KatoJ, Lee TY, Shi C
S- Editor: Ma YJ **L- Editor**: Logan S **E- Editor**: Ma S

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ISSN 1007-9327