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REVIEW

Molecular genetics of gastric adenocarcinoma in clinical practice

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Abstract

The molecular genetics of gastric carcinoma (GC) dictates their biology and clinical behavior. The two morphologically distinct types of gastric carcinoma by Lauren classification, *i.e.*, intestinal and diffuse cell types, have a significant difference in clinical outcome. These two types of GC have different molecular pathogenetic pathways with unique genetic alterations. In addition to environmental and other etiologies, intestinal type GC is associated with *Helicobacter pylori* (*H. pylori*) infection and involves a multistep molecular pathway driving the normal epithelium to intestinal metaplasia, dysplasia, and malignant transformation by chromosomal and/or microsatellite instability (MSI), mutation of tumor suppressor genes, and loss of heterozygosity among others. Diffuse type shows no clear causal relationship with *H. pylori* infection, but is commonly associated with deficiency of cell-cell adhesion due to mutation of the E-cadherin gene (*CDH1*), and a manifestation of the hereditary gastric cancer syndrome. Thus, detection of *CDH1* mutation or loss of expression of E-cadherin may aid in early diagnosis or screening of diffuse type GC. Detection of certain genetic markers, for example, MSI and matrix metalloproteinases, may provide prognostic information, particularly for intestinal type. The common genetic alterations may offer therapeutic targets for treatment of GC. Polymorphisms in Thymidylate synthase to metabolize 5-fluorouracil, glutathione S-transferase for degradation of Cisplatin, and amplification/overexpression of human epidermal growth factor receptor 2 targeted by monoclonal antibody Trastuzumab, are a few examples. P13K/Akt/mTOR pathway, c-Met pathways, epidermal growth factor receptor, insulin-like growth factor receptor, vascular endothelial growth factor receptor fibroblast growth factor receptor, and micro RNAs are several potential therapeutic biomarkers for GC under investigation.

Key words: Molecular genetics; Lauren classification; Intestinal type gastric cancer; Diffuse type gastric cancer; Molecular Biomarker

Core tip: Intestinal and diffuse cell types of gastric carcinoma have a significant difference in clinical outcome with different molecular pathogenetic pathways. Intestinal type gastric carcinoma (GC) is associated with chromosomal and/or microsatellite instability, mutation of tumor suppressor genes, and loss of heterozygosity. Diffuse type GC is commonly associated with mutation of the E-cadherin gene, and a manifestation of the hereditary gastric cancer syndrome. Detection of certain mutations may aid in early diagnosis, screening, and prognostication of GC, and common genetic alterations may offer therapeutic targets for treatment. Furthermore, potential therapeutic biomarkers for GC are under investigation and may hold future promise.

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INTRODUCTION

Gastric carcinoma (GC) is the second major leading cause of cancer-related death and fourth most common cancer worldwide[1]. The relatively unfavorable outcome is largely attributable to complex biology and marginal effectiveness of treatment options, including surgical resection, chemotherapy, and multidisciplinary approach. Even with use of multimodality approaches, overall survival continues to be poor with 30%-36% 5-year survival rates[2,3]. Chemotherapy is the main treatment in cases of metastatic disease, and the median survival time is only 9 to 14 mo[3,4]. However, not all of GCs have the same outcomes. The biological behavior and clinical presentation of GCs differ with their histological and molecular features.

The current World Health Organization classification (2010 edition), classifies GC into many different types based upon the histology combined with molecular genetic information. However, the traditional Lauren classification, purely on histologic basis, is the most commonly used system. It classifies GC into three different groups: (1) intestinal type with glandular differentiation or pattern; (2) diffuse, or poorly differentiated type, including a signet ring cell histology; and (3) mixed or indeterminate type[5]. The first two types of GCs (intestinal and diffuse types) have distinct histogenesis as well as clinical characteristics. Recent data suggest that these two groups largely differ in their molecular genetics. This paper will mainly review the molecular characteristics of non-hereditary intestinal and diffuse types of GC to understand the molecular pathways involved in GC development and to identify molecular targets for diagnosis, therapy, and prognostication.

MOLECULAR BASIS OF PATHOGENESIS

Genetic predisposition of GC

Certain genetic polymorphisms are predisposed to an increased risk for gastric cancer. These polymorphisms were found in genes involved in the inflammatory response to *Helicobacter pylori* (*H. pylori*) infection[6-8], prevention of DNA to oxidative damage[9], and mucosal protection against *H. pylori* infection[10-12], and detoxification[13,14]. Polymorphisms of the interleukin 1 (*IL-1β*) gene consistently show strong association with GC[15]. The association is also seen with other genes, including IL-1 receptor antagonist genes[15-19], tumor necrosis factor-alpha gene[18,20,21], rs11556218 T/G polymorphism of the *IL-16* gene[8], and genes encoding glutathione-S-transferase (GST) (GSTT1 and GSTM1)[22,23]. Many hereditary tumor syndromes increase the risk to develop GC. The high risk association is well-documented in Hereditary diffuse-type gastric cancer syndrome, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Peutz-Jeghers syndrome, Juvenile polyposis and Li-Fraumeni syndrome[24,25].

Molecular pathogenesis of intestinal cell type of GC

The major etiology of the intestinal type includes dietary, environmental factors, and *H. pylori* infection[26]. There are many good reviews that have discussed the role and significance of dietary habits and environmental factors in gastric carcinogenesis, but *H. pylori* infection has also been shown to emerge as an important carcinogen in the stomach. The bacterial virulence factors of *H. pylori* contributing to GC risk include vacuolating cytotoxin A (vacA), blood group antigen binding adhesion 2, outer inflammatory protein, and cytotoxin-associated gene product (*cagA*) genes[27,28]. Infection with a cagA-positive *H.pylori* strain in comparison with a cagA-negative strain increases the risk for development of GC[29]. CagA is translocated into host cells and induces a growth factor-like response in gastric epithelial cells by forming a physical complex with the Src homology 2 domain-containing tyrosine phosphatase in a phosphorylation dependent manner[30,31]. In addition, aberrant expression of activation-induced cytidine deaminase, a gene originally linked to immunoglobulin class switching and B lymphocyte hypermutation, results in accumulation of mutations in the p53 tumor suppressor gene[31,32]. A second virulence gene, the vacA, induces gastric epithelial cell apoptosis and interferes with T cell activation which suppresses local immune response[33]. Chronic inflammation also causes genetic instability through the generation of reactive oxygen and nitrogen species which can directly damage the genomic and mitochondrial DNA[31,34].

The development of GC is a multi-step process. Chronic or atrophic gastritis may lead to intestinal metaplasia, subsequently dysplasia, and eventually carcinoma in some patients[26,35]. During the above progression, a series of genetic alterations occur. The inactivation of tumor suppressor gene p53 is involved in early carcinogenesis, and is found in 38% of intestinal metaplasia, 58% of dysplasia, and 38%-71% of GC[36-38]. Mutations occur more commonly in CpG sites of p53 and transition of G:C to A:T at these sites is the most common type of mutation irrespective of the histologic type of GC[39]. Mutation of p73, a member of the p53 family, is indicated in the carcinogenesis of GC associated with *H. pylori* infection in the mouse model[40].

Chromosomal instability in intestinal-type GC includes gains at 8q, 17q, 20q and losses at 3p and 5q[28,41,42]. Microsatellite instability-high is often seen in intestinal type of GC, largely due to epigenetic effect, (*i.e.*, hypermethylation of the promoter regions of mismatch repair genes, most commonly mutL homolog 1 and mutS homolog 2, and in small percentage of cases, gene mutations[43-45]. The CpG island methylator phenotype was found in 24%-47% of GC, similar to colorectal cancer[43,46-48]. Recent studies have conducted a genome-wide search to identify novel methylation-silenced genes in GC[49,50]. GC cell lines were treated with a demethylating and/or deacetyling agent and were screened for epigenetically silenced genes using oligonucleotide microarrays[49]. The gene encoding serine proteases inhibitor Tissue Factor Pathway Inhibitor 2 was found to be highly methylated (81%) in GC, and its methylation was a significant and independent prognostic indicator in GC[31,49].

Loss of heterozygosity (LOH) or mutation of Adenomatous polyposis coli (*APC*) gene may be found in approximately 25% of the cancer precursors, adenomas, and in up to 60% of intestinal-type GC[51-53]. Mutation of *CTNNB1*, which encodes β-catenin, appears to be exclusive to the mutations that inactivate APC protein[54]. β-catenin accumulates in the cytoplasm, binds to members of the Tcf/Lef family of transcription factors, and is translocated to the nucleus where the Tcf/β-catenin complex activates target genes such as MYC and cyclin D1 gene[31,54]. The incidence of *CTNNB1* mutations in intestinal- *vs* diffuse-type GC remains unclear. One study reported no mutations in diffuse-type GC but 27% incidence in intestinal-type GC[55]. Clements *et al*[56] 2002 found that 26% of tumors with β-catenin nuclear staining contained *CTNNB1* mutations, with no difference between diffuse- and intestinal-type GC.

LOH at the bcl-2 locus and amplification of cyclin D1 and E genes are also associated with intestinal-type GCs[57,58]. The oncogene ErbB2 (Her-2/neu) is amplified in approximately 20% of intestinal type GCs[59]. E-cadherin gene (*CDH1*) mutations have an insignificant association with the development of intestinal-type GC, in contast to diffuse type GC[60,61].

RUNX3 is now accepted as a tumor suppressor gene and first reported in gastric epithelial cells of RUNX3 knockout mice in 2002[62]. Approximately 45%-60% of human GCs show loss of RUNX3 expression due to hemizygous deletion and hypermethylation of the promoter region, and RUNX3 hypermethylation is seen in *H. pylori* infection, intestinal metaplasia, and gastric adenoma[31,62,63]. In response to transforming growth factor (TGF)-β, RUNX3 inhibits gastric epithelial proliferation by inducing the CDKN1A (*p21*) gene[64] and also upregulates the expression of proapoptotic gene BCL2L11 (Bim) in gastric cancer cells treated with TGF-β[65]. Restoration of RUNX3 also strongly inhibited peritoneal metastases of GC in an animal model[66]. RUNX3 inhibited the expression of vascular endothelial growth factor A (VEGF-A) and suppressed angiogenesis and metastasis of GCs[67].

Molecular pathogenesis of diffuse type GC

Little is known about the etiology of diffuse type GC. Epidemiological studies did not link *H pylori* infection to diffuse type of GC. Its association with hereditary gastric cancer predisposition syndrome is well-documented[68]. The unique molecular genetics of this type of GC, in contrast to intestinal-type, is deficiency of the cell-cell adhesion due to genetic or epigenetic inactivation/down regulation of E-cadherin gene (*CDH1*). Approximately 50% of diffuse-type GC harbor this mutation or inactivation[24,69]. The abnormality of *CDH1* gene can be found in early stage of diffuse GC development and loss of E-cadherin expression is seen in invasive and *in situ* carcinomas[70]. In a model proposed by Carneiro *et al*[70], the development of diffuse GC in E-cadherin mutation carriers encompasses *in situ* signet ring carcinoma with pagetoid spread of signet ring cells as pre-invasive lesions. In early hereditary GC, the wild-type CDH1 allele is suppressed or lost in tumor cells with a second hit caused by promoter hypermethylation of CDH1 in at least 50% of cases[71]. Promoter methylation is also part of the major mechanism underlying E-cadherin downregulation in sporadic diffuse gastric cancers[60]. Chromosomal instability in diffuse-type GC include gains at 12q, 13q and losses at 4q, 15q, 16q, and 17p[28,42,72,73]. The diffuse type GC is also associated with the alterations or mutations in other genes or gene products, including the met proto-oncogene encoding the hepatocyte growth factor receptor and the SC-1 antigen (an apoptosis receptor)[74-76].

Molecular pathogenesis of Epstein-Barr virus-associated GC

Five percent of GC is associated with monoclonal proliferation of Epstein-Barr virus (EBV)-infected epithelial cells and is a specific clinicopathologic subset with characteristics of younger age, male predominance, proximal location, lower rate of lymph node involvement, marked lymphocytic infiltration, and lace pattern within the mucosa[31,77]. EBV maintains its latent infection and expresses viral latent genes which include EBV-determined nuclear antigen 1, EBV-encoded small RNA, latent membrane protein 2A (LMP2A) and Bam H1-A rightward transcripts (BARTs)[31,78]. Frequent loss of p16 (CDKN2A), smad4, Fhit, and CD82 (KAI-1) are seen[79]. Global CpG island methylation in the PTEN promoter region is considered as a characteristic abnormality in EBV-associated GC[80] with viral LMP2A responsible for aberrant hypermethylation by activation of host DNA methyltransferase 1[81]. LMP2A also upregulates Birc5 (survivin) expression through the activation of nuclear factor-κB, activates extracellular signal regulated kinases (ERK/MAPK1), and inhibits TGF-β-induced apoptosis through activation of the Ras/PI3K/Akt pathway[31,82-84].

GENETIC CHANGES ASSOCIATED WITH MUCIN PHENOTYPIC EXPRESSION IN GC

GC can be classified into four phenotypes according to mucin (MUC1, MUC2 and CD10) expression: gastric or foveolar phenotype (G-type), intestinal phenotype (I-type), intestinal and gastric mixed phenotype and neither gastric nor intestinal phenotype[31,85]. Genetic changes associated with mucin phenotypic expression in GC include *TP53* mutations in I-type GC and microsatellite instability in G-type. Specific epigenetic alterations include methylation of hMLH1 occurring more frequently in MUC2-negative GC and more frequently methylated MGMT in MUC2-positive GC than in MUC2-negative GC[31,85].

MOLECULAR DIAGNOSIS OF GC

Genetic markers associated with the development of GC are numerous. However, very few have diagnostic utility. CDH1 probably is the best candidate marker for such purpose. About 50 of diffuse type of GC have *CDH1*

mutation, either complete or partial deletions of exons, in more than 70% of somatic E-cadherin mutations[24,68]. This unique gene alteration may have a diagnostic potential. *CDH1* mutations can be detected by polymerase chain reaction on paraffin-embedded tissue. Detection of the germline mutation in CDH1 may help identify asymptomatic mutations carriers of hereditary gastric cancer syndrome and provide molecular basis for prophylactic total gastrectomy[86].

Molecular prognostication

Currently clinical stage is considered to be the gold standard to predict clinical behavior and the most valuable prognostic factor for all GC types. However, clinical stage does not address the issue of tumor heterogeneity. Many studies have investigated molecular biomarkers as alternatives or supplements to the current staging system. There is some success in identifying biomarkers potentially useful in predicting prognosis and therapeutic response.

Microsatellite instability-high is commonly seen in GC located in the distal stomach or antrum, usually intestinal type. It is less frequently associated with metastasis to local lymph nodes[45,87,88]. However, it is still controversial whether patients with MSI-H GC have a favorable long term survival than those with microsatellite instability-low or microsatellite stability GCs[89,90].

Overexpression of matrix metalloproteinases (MMPs) is shown to be related to tumor invasiveness and metastasis[91]. MMP-1-overexpression in GCs has a worse prognosis than tumors without MMP overexpression. VEGF overexpression is associated with shorter survival time attributable to its enhancement of tumor angiogenesis. Amplification or overexpression of cyclin E is correlated with aggressiveness[92]. Amplification/overexpression of the ERBB2 (Her-2/neu) oncogene in general is considered to be an independent, poor prognostic factor[93,94]. Overexpression of EGF-R and abnormal expression of E-cadherin and β-catenin decrease survival or have poor prognosis[95-97]. Abnormal gene expression of IGF2, KIAA1093, OCT2, PCOLCW, PFN2, RBP4, and three genes (*BIK*, *Aurora kinase B* and *eIF5A2*) identified in the primary tumor are related to node metastasis[98,99]. Expression of caudal type homeobox transcription factor 2 (CDX2) and combination of normal expression of E-cadherin and negative expression of the transmembrane protein MUC1 predict a better prognosis for patients with GC[100,101]. Down-regulation of a cyclin dependent kinase inhibitor, P27/Kip1, is a negative prognostic factor[102,103]. Loss of expression of tumor suppressor gene Rb is related to worse overall survival or inversely correlates with tumor invasion[104,105]. Mutation or abnormal expression of p53 may have a reduced cumulative survival, lymph node metastasis, and lower chemosensitivity[100,106,107], but its overall prognostic significance is controversial[108]. Protection of telomere expression levels are also higher in advanced GC[28].

Molecular therapeutic predicators

The management of patients with GC, particularly those in late stage of tumors, usually requires chemotherapy or target therapy as single or one of the components of combined modality. The chemotherapy or target therapy is toxic, and the effectiveness is variable with patients. Molecular biomarkers have been proven to be a useful tool to predicate therapeutic response and may be used clinically to select patients or chemotherapeutic regimen for optimal result.

Predictors for Fluorouracil treatment: (1) Thymidylate synthase (TYMS) is a catabolizing enzyme for fluorouracil (5-FU). Polymorphisms in the gene encoding TYMS affect expression and appear to be associated with poorer response with 5-FU (47 marker) levels[109,110]. A specific polymorphism in the 5'-untranslated regions is correlated with low sensitivity to 5-FU based chemotherapy and decreased survival in a retrospective study[111]; (2) Dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP) are two regulatory enzymes involved in the degradation of 5-FU. Low levels of DPD and TP have been shown to be associated with better response[24,112,113]; and (3) The role of other genes or products for predicting 5-FU response has been also investigated, but results are inconclusive. These molecular markers include glutathione S-transferase (GST), vascular endothelial growth factor, and apoptosis-related genes and gene products including Bcl-2, Bax and p53[43,114,115].

Molecular predictors for Cisplatin treatment: Unlike for 5-FU, molecular predicting markers for chemosensitivity of Cisplatin are not well established. GST, an enzyme that degrades Cisplatin, is one of the potential markers. Its activity is affected by polymorphisms in the *GSTM1*, *GSTT1*, and *GSTP1* genes, which may in turn cause variable catabolism of Cisplatin and prognosis[111,116,117]. GC with a high LOH rate or MSI-high show a better response to a Cisplatin-based chemotherapy[118].

Molecular targeted therapy: Trastuzumab is a monoclonal antibody targeting HER-2 that has shown an overall survival benefit when combined with palliative chemotherapy in patients with HER-2 amplified GC[119]. HER-2 is currently the only validated therapeutic target in GC with guidelines for HER-2 testing established by the ToGA trial[119].

HER-2 expression may be assessed by immunohistochemistry (IHC), with scoring ranging from 0 to 3+, by gene amplification using fluorescence in situ hybridization (FISH) or by silver in situ hybridization[28,119]. The survival benefit associated with trastuzumab is seen greatest in IHC 3+ or IHC 2+ and FISH-positive patients. Complete membranous staining is not a prerequisite for IHC 2+ or IHC 3+ scores in GC as it is for breast cancer since gastric tumor cells may only show HER-2 staining at the basolateral or lateral membrane regions[28,120].

Other potential candidates for targeted GC therapy include P13K/Akt/mTOR pathway, c-Met pathways, epidermal growth factor receptor (EGFR), VEGF receptor, insulin-like growth factor receptor, and fibroblast growth

factor receptor[121].

Lapatinib is a dual kinase inhibitor of EGFR and HER-2 under investigation in two ongoing phase Ⅲ clinical trials in a select group of patients positive HER-2[121]. These include the Lapatinib Optimization Study in HER-2 Positive Gastric Cancer study with capecitabine and cisplatin in the first-line setting and the TYTAN study in second-line therapy using paclitaxel[121-123].

In terms of other agents, targeting human EGFR in GC remains controversial. Cetuximab is targeted against EGFR and is a recombinant human, chimeric IgG1 monoclonal antibody[121,124]. With combined chemotherapy and cetuximab, promising results have been shown in a phase Ⅱ trial, but when compared to chemotherapy, the EXPAND study (phase Ⅲ) failed in prolonging the progression free survival (PFS) and overall survival[125]. The REAL-Ⅲ trial did not show any advantage of adding panitumumab to a combination of chemotherapy and also showed a worse overall survival and PFS[126-128]. The combination with matuzumab and chemotherapy seems more promising but was evaluated only in phase Ⅱ trials[129]. Thus, additional studies are necessary.

Antiangiogenic therapy has shown minimal effectiveness when compared to existing treatments for GC[130,131]. Biomarkers such as serum VEGF-A and microvessel density still remain unconfirmed as potentially useful predictive markers by phase Ⅲ trials[121]. However, in advanced cases of GC treated with the VEGF inhibitor bevacizumab, plasma VEGF-A and tumor neuropilin-1 are strong biomarker candidates for predicting clinical outcome[132].

Various ongoing trials are testing potential targeting agents addressed to the downstream components of VEGF-R/EGFR, such as inhibitors of mTOR, c-Met, and Histone deacetylase[121]. The phase Ⅲ trial (GRANITE-1) of everolimus, an inhibitor of the P13K/Akt/mTOR pathway, has reported prolonged PFS with a 34% reduction of the risk of progression[121,133].

MICRORNAS AS THERAPEUTIC TARGETS

In recent years, microRNAs (miRNAs) have been investigated as potential markers in treatment of GC. MiRNAs are important regulators of genes with critical roles in cell proliferation, differentiation, and survival[134]. MiRNAs play important roles in the pathogenesis of a variety of malignancies[135-139]. Different miRNA methylation profiles are seen in various cancers. MiR-155 is down-regulated and methylated in GC[140]. MiR-155 is up-regulated in breast cancer[141], colorectal cancer[142] and pancreatic ductal adenocarcinoma[143]. Upregulated miRNAs might act as oncogenes and target tumor suppressors, while down-regulated miRNAs might act as tumor suppressors and target oncogenes[144]. Several miRNAs have been found to be deregulated in GC but the specific molecular mechanisms are unknown[144]. DNA hypermethylation in the miRNA 50 regulatory region accounts for the downregulation of miRNA in tumors[145,146], and many miRNAs have been reported to be down-regulated due to hypermethylation of the CpG islands in GC. MiR-124a-1, miR-124a-2 and miR-124a-3 have been found to be methylation-silenced in GC cell lines[144,147]. Such epigenetic changes are reversible, and make them a potential therapeutic target. Silenced miRNAs in GC could be restored by treating with demethylating agents, such as decitabine (5-aza-20-deoxycytidine), which leads to inhibition of growth, invasion, and metastasis of GC cells[148].

Interestingly, studies have shown that the miRNA methylation levels are positively associated with the clinical stage of GC patients[144]. Low expression of miR-34b and miR-129-3p are associated with a poor clinical outcome of GC patients, and hypermethylation of miR-129-2 and miR-34b CpG islands had a tendency to show poor clinicopathological features[144,149]. Thus, specific miRNA methylation levels may be used in the prognosis of GC patients. However, limitations exist as several factors besides methylation can affect miRNA expression levels. As reported by Tsukamoto *et al*[148], the expression of miR-375 in NUGC3 cells can be significantly increased with either 5-aza-2-deoxycytidine and markedly up-regulated by greater than 20-fold when treated with both 5-aza-2-deoxycytidine and trichostatin A[148]. In addition, *H. pylori* infection can induce aberrant DNA methylation in gastric epithelial cells[150]. Individuals with *H. pylori* had 7.8-13.1-fold higher methylation levels than those without *H. pylori* infection[147,151]. Another limitation is the serious side effects of demethylating drugs. The use of demethylating agents may induce the expression of many otherwise normally silenced genes and cause a variety of diseases. Thus, the use of demethylating agents in restoring the expression of epigenetically silenced miRNA in GC still requires further investigation.

CONCLUSION

The current research has provided some insights to the genetics of gastric cancer. Clinical trials based upon the genetic information have generated promising results. However, up to date, we still do not have an optimal solution for prevention, early diagnosis, and treatment of this disease. The advanced molecular technology, particularly next generation sequencing, may offer hope in deciphering the myth behind the molecular genetics of gastric cancer. Equipped with the advanced technology, together with efforts from clinical oncology and bioinformatics, we have gradually gained much more understanding about the genetic basis of the host-environmental interaction and will have a greater opportunity to identify diagnostic and therapeutic markers for gastric cancer. These advancements have shed light in finding a cure for gastric cancer in the near future.

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