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Mutational landscape of TP53 and CDH1 in gastric cancer

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Abstract

In this editorial we comment on an article published in a recent issue of the *World J Gastrointest Surg*. A common gene mutation in gastric cancer (GC) is the TP53 mutation. As a tumor suppressor gene, TP53 is implicated in more than half of all tumor occurrences. TP53 gene mutations in GC tissue may be related with clinical pathological aspects. The TP53 mutation arose late in the progression of GC and aided in the final switch to malignancy. CDH1 encodes E-cadherin, which is involved in cell-to-cell adhesion, epithelial structure maintenance, cell polarity, differentiation, and intracellular signaling pathway modulation. CDH1 mutations and functional loss can result in diffuse GC, and CDH1 mutations can serve as independent prognostic indicators for poor prognosis. GC patients can benefit from genetic counseling and testing for CDH1 mutations. Demethylation therapy may assist to postpone the onset and progression of GC. The investigation of TP53 and CDH1 gene mutations in GC allows for the investigation of the relationship between these two gene mutations, as well as providing some basis for evaluating the prognosis of GC patients.

Key Words: TP53; CDH1; Gastric cancer; Gene mutation; Methylation

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Core Tip: The separation of TP53 and CDH1 mutations in gastric cancer (GC) demonstrates their separate processes. Mutations in TP53 are linked to advanced-stage cancers and a poor prognosis, whereas CDH1 mutations are linked to widespread GC. This work emphasizes the variability of GC and sheds light on prospective targeted therapeutics based on distinct mutation patterns. Understanding the mutational landscape of TP53 and CDH1 can help to develop tailored therapy strategies for GC patients.

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INTRODUCTION

Gastric cancer (GC) is the fifth most prevalent malignant tumor in the world and the third greatest cause of death[1]. GC is prevalent in Asia, particularly in Japan and China[2]. The incidence of stomach cancer has decreased over the last decade, presumably because of improvements in hygiene, better nutrition awareness, dietary changes, and the elimination of *Helicobacter pylori* infection. Currently, surgery combined with adjuvant chemotherapy is the principal treatment for GC, with surgical resection and routine lymph node clearance being the gold standard for treatment[3]. GC has a complicated etiology that is often the product of numerous factors[4]. One of the variables that contribute to the development of cancer is genetic mutations, and different mutant genes can be discovered in different stomach cancer tissue samples[5]. Even when the same gene mutation occurs in multiple patients, the manner it expresses itself varies. The link between various genes and stomach cancer varies as well. Gastric carcinoma is a multigene, multifactor, and multistage process that is thought to be the result of interactions between environmental and genetic factors[6]. Smoking, alcohol consumption, a high salt diet, and infection with *H. pylori* and Epstein-Barr virus are all risk factors. The natural dynamic equilibrium between cell proliferation and death in gastric mucosal cells is broken throughout the development from chronic gastric inflammation to GC, resulting in genetic abnormalities. Cancer-related genes linked to GC include the RAS gene, the HER2 gene, c-myc, and bcl-2[7]. Tumor suppressor genes such wild-type TP53, APC, and DCC are shut down[8]. Gastric epithelial cells proliferate excessively without beginning apoptotic signals, eventually leading to GC.

TP53 AS AN IMPORTANT TUMOR SUPPRESSOR GENE

As a tumor suppressor gene, TP53 is implicated in more than half of all tumor occurrences[9]. The TP53 gene, which is separated into two types: Wild-type and mutant-type, protects genomic stability and is the gene most closely connected with cancers in recent years[10]. The TP53 gene was found in 1979, and because it is abundantly expressed in tumor tissues but not in normal cells, it was classified as an oncogene. The wild-type TP53 gene was eventually confirmed to be a tumor suppressor gene through tests in 1989[11]. The TP53 gene, which encodes a nuclear phosphoprotein with 393 amino acid residues and is named after its molecular weight (53 KD), is located on the short arm of chromosome 17, specifically on 17p13.1. The TP53 gene is made up of 11 exons and 10 introns, and it is translated into a 2.5 kb mRNA in all cells. The TP53 gene is essential for cell cycle arrest, aging, apoptosis, differentiation, and metabolism. TP53 gene mutations are found in more than 50% of tumors[12].

TP53 ENCODING P53

The tumor suppressor gene TP53 has been implicated in cancer, and the p53 protein expressed by it is an important regulatory component in normal cellular physiology[13]. The p53 protein regulates cell senescence, occurs later in the cell cycle, and regulates DNA repair[14]. More significantly, when gene damage is substantial and cannot be corrected, it might promote cell apoptosis. p53 now mediates cell apoptosis by activating mitochondrial and death receptor-induced apoptotic pathways[15]. The p53 protein is essential in the biological response to DNA damage by inducing apoptosis or growth arrest in proliferating cells[16]. DNA damage disturbs cell homeostasis by activating or amplifying particular metabolic processes that regulate cell growth and division, potentially leading to multicellular organism degeneration and aging[17]. According to research, TP53 can attach to enhancer sites in healthy fibroblasts and be rapidly activated in response to DNA damage[18]. TP53, the most essential tumor suppressor, preserves the genome by coordinating different DNA damage response pathways. TP53 is the primary mediator of DNA damage repair activities such as nucleotide excision repair, base excision repair, mismatch repair, nonhomologous end-joining, and homologous recombination[19]. If DNA damage is not repaired in a timely manner, p53 will activate the transcription of apoptosis-inducing genes, finally leading to cell death.

TP53 MUTATION AND TUMORS

When cells are driven by hazardous substances such as ionizing radiation, the wild-type TP53 gene is activated, causing the cell proliferation cycle to stall at the G1 phase and therefore delaying cell cycle progression[20]. At this point, the TP53 gene transcriptional activity is increased, prompting the activation of the p21 gene, which is a direct downstream target gene of TP53[21]. The p21 gene suppresses cyclin-dependent kinase activity, inhibiting continued cell proliferation[22]. If TP53 gene alterations are caused by a variety of reasons, the gene will lose its surveillance function on cells, and damaged DNA will enter the next cycle of cell proliferation, resulting in mutations or chromosomal abnormalities[23]. Mutated TP53 genes lose their inhibitory action and increase the ability to promote malignant transformation, resulting in tumor formation and progression[24]. TP53 mutations not only cause tumor suppressor function loss in some tumor cells, but also accelerate tumor cell growth and development and the acquisition of novel oncogenic characteristics[25]. The majority of TP53 mutations are missense mutations and gene deletions generated by single nucleotide substitutions, which alter TP53 gene activity[26]. The TP53 gene, in its wild-type form, regulates the cell cycle, mediates DNA damage repair, and induces apoptosis. Mutant p53 not only loses the tumor suppressor function of wild-type p53, but it also increases tumor cell activity, invasion, and metastasis, boosting tumor incidence and progression[27].

TP53 MUTATION AND GC

More than half of all human malignancies involve TP53 inactivation. A tumor may include several mutations, resulting in p53 mutation status heterogeneity. A common gene mutation in GC is the TP53 mutation. According to different findings, the TP53 mutation rate in GC varies, and TP53 gene mutations in GC tissue may be related with clinical pathological aspects such as tumor staging, lymph node metastasis, prognostic indicators, and treatment evaluation[28]. Approximately 95% of functional mutations occur in the chromosomal region encoding the p53 sequence specific DNA binding domain[29]. These mutations disturb the coding sequence natural conformation, accelerate the buildup of DNA damage in cells, and hence cause cancer.

TP53 MUTATION AND GC PROGRESSION

Gastric mucosal intestinal metaplasia (IM) is a precancerous lesion associated with GC. According to the data, we discovered that the expression level of p53 gradually increased with the progression of the disease from normal gastric mucosa to GC by detecting TP53 gene mutation and p53 protein expression in normal gastric mucosa, IM without GC, IM with GC, and GC[30]. Furthermore, TP53 mutation was not found in IM, but it was found in GC at a high incidence, suggesting that TP53 mutation occurred in the late stage of GC and aided in the final transition to cancer. Lauren's classification divides GC into three types: Intestinal type GC, diffuse-type GC, and mixed-type GC. As one of the major risk factors for GC, *H. pylori* infection is thought to be the most dangerous for intestinal type GC[31]. According to certain studies, enhanced p53 protein expression has been found in the stomach mucosa of *H. pylori*-infected patients with precancerous lesions[32]. The most recent research indicates that when *H. pylori* infects the gastric mucosa, it causes an inflammatory response, resulting in hypermethylation of DNA in the promoter region of the upstream stimulating transcription factor gene USF1, which reduces its expression[33]. Because USF1 collaborates with the TP53 gene to maintain genetic stability, it will reduce p53 levels, impacting signal transmission, DNA repair, and cell cycle regulation. *H. pylori*-infected gastric mucosa has a diminished ability to repair DNA, compromising genetic stability and eventually contributing to tumor formation.

CDH1 ENCODING E-CADHERIN

CDH1, also known as calcium-dependent cell adhesion molecule, is a tumor suppressor gene found on chromosome 16q22.1[34]. It is a calcium-dependent cell adhesion molecule, and its transcription produces a 4.5 kb mRNA from 16 exons. It encodes for epithelial cadherin (E-cadherin), which is involved in cell-to-cell adhesion, epithelial structure maintenance, cell polarity, differentiation, and intracellular signaling pathway regulation[35]. The extracellular peptide section, the transmembrane region, and the intracellular peptide segment make up E-cadherin[36]. The HAV sequence recognizes and mediates cell-to-cell adhesion, whereas the intracellular peptide segment is linked to the cytoskeleton of actin filaments *via* various linking proteins (such as catenin and p120), providing cellular structural attributes that regulate cell signaling[37]. E-cadherin is a cell adhesion protein that plays a significant role in the integrity of epithelial tissue shape and function, as well as inhibiting tumor cell invasion and metastasis[38]. A decrease in cell adhesion enhances tumor cell migration and is one of the main elements contributing to the occurrence and progression of tumors [39].

CDH1 MUTATION AND EPITHELIAL MESENCHYMAL TRANSITION

Cell polarity is diminished and migratory and invasive growth capabilities are enhanced when E-cadherin is downregulated in epithelial cells. E-cadherin loss stimulates signaling pathways, resulting in epithelial mesenchymal transition (EMT)[40]. Several signaling pathways, including the Wnt signaling pathway, Rho GTPases, and the epidermal growth factor receptor (EGFR), are known to play a favorable role in EMT through diverse E-cadherin interaction patterns and connections with cell adhesion complexes and the actin cytoskeleton[41]. Wnt signaling can activate Wnt target genes such as CD44, c.MYC, Cyclin D1, and matrix metalloproteinase 7, promoting tumor cell proliferation and progression[42]. Extracellular CDH1 missense mutations associated with HDGC have been reported in studies to boost RhoA activity, improving tumor cell migratory capability[43]. EGFR is also involved in the activation of RhoA *via* the E-cadherin-dependent pathway. Mutations in E-cadherin's extracellular domain may disrupt the connection between E-cadherin and EGFR, resulting in EGFR activation and increased tumor cell activity *via* RhoA activation[44]. These methods suggest that inactivating E-cadherin can disrupt associated signaling pathways and contribute to the advancement of EMT and GC [45].

CDH1 MUTATION AND DIFFUSE GC

CDH1 mutations and functional loss can lead to the development of diffuse GC (DGC), and CDH1 mutations can be used as independent prognostic variables in DGC. E-cadherin inactivation is linked to somatic CDH1 gene mutations, promoter methylation, overexpression of transcriptional suppressors, and heterozygous deletion in DGC. DGC is predisposed to persons who have sporadic or inherited CDH1 gene mutations[46]. CDH1 mutations occur at a rate of about 25% in sporadic DGC and can approach 50% in hereditary DGC (HDGC)[47]. Liu *et al*[48] found the mutation rates of 32 genes, including TP53, SPEN, FAT1, and CDH1 exceeded 10%. Besides, CDH1 mutations were significantly associated with DGC. CDH1 germline mutations affect the whole coding sequence as well as the protein's functional domains. Short insertions and deletions are the most prevalent mutation types, accounting for around 35% of all mutations. Other types of mutations include missense (28%), nonsense (16%), splice site variations (16%), and substantial exonic deletions (5%).

CDH1 MUTATION AND HDGC

Guilford *et al*[49] detected truncating mutations in three pedigrees of a Maori family in New Zealand in 1998, demonstrating an autosomal dominant inheritance pattern of early-onset DGC. This important study was the first to show that CDH1 mutations cause HDGC. HDGC accounts for 1%-3% of gastric malignancies, and CDH1 gene alterations cause 30%-40% of reported HDGC cases[50]. These mutations have been found in populations of many racial backgrounds, including Europeans, Africans, Japanese, Koreans, and Chinese. Following methylation, mutation, or heterozygous deletion of the second allele of E-cadherin, CDH1 in HDGC is inactivated[51].

THE ASSOCIATION OF CDH1 MUTATIONS WITH PROGNOSIS

Furthermore, studies suggest that CDH1 mutations are linked to a poor prognosis in HDGC[52]. Moslim *et al*[52] discovered that HDGC patients who did not have detectable CDH1 mutations prior to surgery were more likely to develop metastasis and die from the disease than patients with known mutation status, implying that genetic counseling and CDH1 mutation testing can improve the survival rate of GC patients, particularly those with DGC. Males with CDH1 mutations are projected to have a 70% lifetime risk of having stomach cancer by the age of 80, while females have a 56% lifetime risk. The International Gastric Cancer Association has developed criteria for testing CDH1 gene mutations based on these conditions: (1) Regardless of age, having 2-3 cases of GC in first- or second-degree relatives, with at least one confirmed case of DGC; (2) No family history, but diagnosed with DGC before the age of 40; (3) Having both a family history and cases of DGC or lobular breast cancer, with age; and (4) Having both a family history and cases of diffuse gastric. Individuals who satisfy these requirements should be tested for CDH1 gene mutations. These criteria have a sensitivity of 0.79-0.89, a specificity of 0.70, a positive predictive value of 0.14-0.19, and a negative predictive value of 0.97.

CDH1 HYPERMETHYLATION IN GC

Aberrant DNA methylation is a common characteristic of cancer and a critical epigenetic mechanism for regulating gene expression[53]. Table 1 summarizes gene methylation in GC. Tumor suppressor gene hypermethylation and oncogene hypomethylation are two major biological processes implicated in tumor formation and progression. CDH1 hypermethylation has been seen in a variety of cancers, including liver cancer, breast cancer, prostate cancer, ovarian cancer, and GC[54]. In the cancer genome atlas project, gastrointestinal malignancies show the highest frequency of DNA methylation alterations among all reported tumor types[55].

Table 1 Gene methylation in gastric cancer	
Cell process	Gene
Cell cycle regulation	Cyclin E, CDC25B, p27, p53, RB, CHFR, hsMAD2, PRDM5
Cell adherence	CDH1
DNA repair	MLH1, MSH2, PMS2
Invasion and migration	HOXA10, PRL-3
Apoptosis	BNIP3

The wild-type allele of CDH1 is silenced in most cases of HDGC due to excessive methylation in the promoter region, resulting in the loss of its original function[56]. CDH1 promoter hypermethylation has been linked to the development of DGC, resulting in CDH1 silence, reduced E-cadherin expression, and weaker cell adhesion mediated by E-cadherin[57]. Early in the disease, CDH1 promoter hypermethylation can be found in precancerous lesions of the stomach mucosa. As a result, CDH1 promoter hypermethylation may be used to identify people at risk for poorly differentiated, diffuse-type GC[58]. A meta-analysis of CDH1 hypermethylation and GC revealed that CDH1 hypermethylation levels in cancer tissues are significantly higher than normal gastric mucosa, and hypermethylation levels in adjacent normal tissues are also significantly higher than normal gastric mucosa[59]. The process of CDH1 promoter hypermethylation is reversible and is dependent on changes in the tumor microenvironment, implying that demethylation therapy could help delay the onset and progression of GC.

CLINICAL IMPLICATIONS

The investigation of TP53 and CDH1 gene mutations in GC allows for the investigation of the relationship between these two gene mutations and the clinicopathological characteristics and prognosis of patients, as well as providing some basis for evaluating the prognosis of GC patients. In clinical trials, GC patients who satisfy the criteria may be offered a test for TP53 and CDH1 gene mutations. Because the CDH1 promoter hypermethylation process is reversible, the use of demethylating medicines may help to prevent and postpone the onset and progression of GC.

CONCLUSION

In this editorial, we comment on the article “Mutational separation and clinical outcomes of TP53 and CDH1 in gastric cancer”[60]. As a tumor suppressor gene, TP53 is implicated in more than half of all tumor occurrences, and the p53 protein expressed by it is a key regulatory component in normal cellular function. TP53 mutations not only cause tumor suppressor function loss in some tumor cells, but also accelerate tumor cell growth and development and the acquisition of novel oncogenic features. TP53 gene mutations in GC tissue may be related with clinical pathological aspects such as tumor staging, lymph node metastasis, prognostic indicators, and treatment evaluation, according to different findings. The TP53 mutation arose late in the progression of GC and aided in the final switch to malignancy. CDH1 encodes E-cadherin, which is involved in cell-to-cell adhesion, epithelial structure maintenance, cell polarity, differentiation, and intracellular signaling pathway modulation. CDH1 mutations and functional loss can result in DGC, and CDH1 mutations can serve as independent prognostic indicators for poor prognosis. In HDGC, CDH1 mutations are harmful. GC patients can benefit from genetic counseling and testing for CDH1 mutations. CDH1 promoter hypermethylation could be used to identify those at risk for poorly differentiated, diffuse-type GC. Demethylation therapy may assist to postpone the onset and progression of GC.

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