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Molecular Pathogenesis of Gastric Cancer

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Abstract

In this article, I will survey the major genetic susceptibility and somatic genetic alterations involved in gastric cancer and adenoma. These include germline and somatic genetic alterations in oncogenes, tumor suppressor genes, and apoptosis-related genes. A small proportion of gastric cancers arise as a consequence of hereditary predisposition caused by specific germline mutations in E-cadherin, mismatch repair genes, adenomatous polyposis coli, and STK11. Aberrant expression of activation induced cytidine deaminase, triggered by Helicobacter pylori infection, accumulates with genetic mutations of oncogenes and tumor suppressor genes, including p53 and CTNNB1. Inactivation of trefoil factor family 1, which is a gastric specific tumor suppressor, occurs in gastric adenomas and cancers. Ectopic expression of CDX2 leads to intestinal metaplasia and defective Cdx2 expression accelerates the transformation of metaplastic cells to gastric cancer. Genetic alterations of p53 and genes related to Wnt signaling pathway and microsatellite instability occur early in the development of gastric carcinoma, indicating that detection of certain genetic alterations in adenomas may be indicative of malignant transformation. In addition, inactivation of apoptosis-inducing gene caused by mutations may be an escaping mechanism against apoptotic cell death and contribute to the progression of gastric cancer. Although the results of many studies are contradictory with one another, genetic alterations in oncogenes and tumor suppressor genes are present even in gastric adenoma and increase in frequency during multistep gastric carcinogenesis. Genetic alterations described herein, and from as yet unidentified target genes in gastric cancer cells, will guide us towards more effective risk assessment, diagnosis, and treatment.

Keywords: Gastric cancer; Mutation; Oncogene; Tumor suppressor gene; Apoptosis
핵 심 용 어: 위암; 돌연변이; 종양유전자; 종양억제유전자; 세포자멸사

Introduction

Gastric cancer has a high incidence in Asia and is a leading cause of cancer death in the region (1). It accounts for an estimated 20.8% of all malignancies in Korea, 24.5% in males and 15.8% in females. The annual age-standardized incidence of the disease is 68.1 per 100,000 in male, 29.0 per 100,000 in female (2~3). Despite tremendous advances in molecular cancer genetics in past few decades, the exact

molecular mechanism that underlies gastric carcinogenesis is remains unclear. To date, it is well known that Helicobacter pylori (H. pylori) infection, environmental factors, dietary habits, host genetic factors are involved in gastric carcinogenesis (4~6). Of these, chronic H. pylori infection, classified by the WHO as a class I carcinogen since 1994, was relatively well studied (7, 8). The biological plausibility of causal relationship has been confirmed by strong correlation between H. pylori infection and putative precancerous gastric lesions, such as atrophic gastritis and intestinal metaplasia (9), and by production of lesions resembling human gastric cancer in Mongolian gerbils following long-term experimentally induced infection (10). However, only a small fraction of infected individual develops gastric cancer (8). H. pylori infection is likely to influence the risk of gastric carcinogenesis by different genetic polymorphism of host factors, including variants of pro-and anti-inflammatory cytokines such as interleukin (IL) and tumor necrosis factors (TNF) (11). Therefore, gastric cancer is thought to arise from a combination of environmental and host factors, and the accumulation of specific genetic alterations that induce transformation of normal gastric mucosal epithelium to cancer cells.

Gastric cancer can be classified into two main histologic types: intestinal and diffuse, each possesses different clinicopathological characteristics (12). Intestinal-type gastric cancer occurs more frequently in older patients, and is histologically differentiated, exhibits well-defined glandular structures and expanding growth pattern. In contrast, diffuse-type gastric cancer is histologically undifferentiated, exhibits a diffuse infiltrative growth pattern and is more prevalent in young patients. The sequence of intestinal-type gastric cancer is as follows: chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and cancer. This suggests that gastric carcinogenesis can be considered a multi-step process. Unlike intestinal-type gastric cancer, diffuse-type gastric cancer develops following chronic gastritis without going through the intermediate stages of atrophic gastritis and intestinal metaplasia (13).

Malignant neoplasms have several phenotypic attributes, such as proliferation, differentiation, local invasiveness and the ability to metastasize to distant organs. At the molecular level, tumor development and progression most likely result from multiple mutations that occur independently in different cells, generating subclones with varying abilities to grow, invade, metastasize and resist. The estimated total number of genetic events for gastric cancer was 4.18 (14). In normal cells, duplication of the base sequence in nuclear DNA is exceptionally accurate. The overall error rate is one mis-incorporated base for every billion nucleotides polymerized (15). It is well known that the inflammatory process, including chronic infection of gastric mucosa with H. pylori, could drive carcinogenesis by generating reactive oxygen species that are directly genotoxic, and stimulating reparative proliferative processes in the inflamed tissue (16). Generally, activation of the checkpoint pathway, including p53, by DNA-damaging agents or by hypoxia leads to cell cycle arrest at G1 and induction of DNA repair. Alternatively, apoptosis is triggered when DNA damage is too extensive.

The genetic susceptibility and somatic genetic alterations involved in gastric cancer are outlined in this article. Discussions will focus on selected oncogenes and tumor suppressor genes associated with the development and/or progression of gastric cancer, which may play an important role not only in cell proliferation, but also in the cell death control.

Genetic Susceptibility of Gastric Cancer

Most sporadic gastric cancers arise against the background of chronic atrophic gastritis and/or intestinal metaplasia, which is commonly caused by H. pylori infection (17, 18). Familial relatives of gastric cancer patients have a higher risk of cancer, with a high prevalence of H. pylori infection and intestinal metaplasia (19). However, a small proportion of gastric cancers arise as a consequence of hereditary predisposition caused by specific germline mutations. Hereditary diffuse-type gastric cancer with a germline mutation in cell adhesion protein, E-cadherin, has been described in New Zealand (20). One of the larger studies of 18 gastric cancer families of European origin found three families with germline E-cadherin mutation in diffuse-type gastric cancer, and incomplete penetrance of germline E-cadherin mutation in obligatory carriers who remained unaffected in their eighth and ninth decades (21). Yoon et al. found two germline mutations of the E-cadherin gene in five Korean familial gastric cancer patients (22). In contrast, germline mutations of this gene were not detected in intestinal-type gastric cancer families (21), and sporadic diffuse-type gastric cancer patients in Britain (23). Therefore, it appears that germline mutations in E-cadherin are rare in Korean gastric cancer patients.

Hereditary non-polyposis colorectal cancer (HNPCC) is also an inherited predisposition syndrome associated with gastric cancer development (24). HNPCC patients inherit germline mutation in one of the DNA mismatch repair genes, leading to defects in the corresponding DNA repair proteins (25). HNPCC-associated gastric cancer was predominantly diagnosed at the mean age of 56, of the intestinal-type, without H. pylori infection and most exhibited microsatellite instability (26). However, there were no differences in polyp growth, H. pylori infection, inflammation, atrophy and intestinal metaplasia between mutation-positive and mutation-negative family members in a Finnish HNPCC registry study. Gastric neoplastic lesions were not found in either group. Therefore, germline mutations of DNA mismatch repair genes are rare in gastric cancer (27).

Gastric cancers may also occur in familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome (PJS) caused by germline mutations of APC and LKB1/STK11 genes, respectively (28~30). Gastric adenomatous polyps may develop in about 10% of individuals with FAP and hamartomatous polyps in the stomach occur in approximately 24% of patients with PJS, but the risk of gastric cancer is low (28). In addition, gastric cancer develops in an extended Li-Fraumeni syndrome associated with germline mutations of the p53 tumor suppressor gene (31).

Somatic Genetic Alterations in Gastric Cancer

1. Helicobacter pylori infection

H. pylori infection is the most common cause of chronic gastritis, which results from increased acid production and disruption of the normal gastric protective mechanism. H. pylori colonization leads to superficial gastritis, chronic atrophic gastritis and intestinal metaplasia and, finally, dysplasia and adenocarcinomas (32) Therefore, gastric cancer is generally believed to be caused by a sequence of events triggered by chronic H. pylori infection. Since H. pylori tends to disappear as intestinal metaplasia and

atrophy develop, and most of those infected with H. pylori do not develop gastric cancer, the exact molecular mechanism of gastric carcinogenesis by H. pylori remains to be elucidated.

Recently, Matsumoto et al. reported that cagPAI-positive H. pylori infection triggered aberrant expression of activation induced cytidine deaminase (AID) in gastric epithelium (33). AID induces class switch recombination that replaces one immunoglobulin heavy-chain constant region gene with another, and somatic hypermutation in non-lymphoid cells as well as in B cells (34, 35). The activities of AID are potentially dangerous to cells, and need to be tightly control-led to avoid mutations in genes that could lead to cancer (36). Its expression resulted in the accumulation of nucleotide alterations in the TP53 tumor suppressor gene and CTNNB1 oncogene, particularly in the transcribed region (33). It is possible to hypothesize that aberrant AID expression caused by H. pylori infection can accumulate with genetic mutations of oncogenes and tumor suppressor genes, including p53 and CTNNB1, in the gastric mucosa which give rise to gastric cancer. In 186 Korean sporadic gastric cancers, AID expression was detected in 73 corresponding normal gastric mucosa and in 50 gastric cancer cells. AID expression was not associated with clinocopathologic parameters, including tumor size, histologic type and lymph node metastasis. However, significant association was observed between AID and the p53 nuclear expression (37).

In addition, it has been reported that H. pylori infection elicits uncontrolled cell proliferation and genetic instability of nuclear and mitochondrial DNAs in gastric cells by down-regulation of the base excision repair and mismatch repair system (38, 39). Taken together, it appears that H. pylori infection, as an early event, plays a role in gastric carcinogenesis. Although gastric adenocarcinoma is closely associated with H. pylori infection, only a small fraction of infected individuals develop gastric cancer (8). Therefore cancer risk is thought to be associated with different H. pylori strains, the inflammatory response governed by host genetics and specific interactions between host and microbial determinants (13).

2. Trefoil Factor Family 1 (TFF1)

TFF domain peptides are small and stable molecules which bear one or two trefoil motifs which have six cystein residues, that form three disulfide bonds and hold the protein in a characteristic three-loop structure (40). In human, three trefoil peptides have been identified: TFF1, produced mainly in the foveolar and superficial epithelium of gastric mucosa (pS2); TFF2, produced in the gastric mucous neck cells and duodenal Brunner's gland (spasmolytic peptide: SP); and TFF3 produced in the goblet cells throughout the intestine (intestinal trefoil factor) (41, 42). All three genes encoding these human trefoil peptides are clustered within a region of 55 kb on chromosome 21q22.3 (43). In our high density loss of heterozygosity (LOH) study, 20 out of 40 (50%) informative carcinomas showed LOH at one or more loci, and peak LOH frequency was identified at D21S1820 (32.4%) in 21q22.3, suggesting that TFF1 might be the possible candidate tumor suppressor gene in this region (44). Interestingly, there is accumulating evidence that TFF1 has tumor suppressor properties, particularly in gastric cancer: I) the expression of TFF1 is reduced in intestinal metaplasia and gastric adenomas (45), and completely lost in 50~60% of gastric carcinoma (46, 47); II) In a TFF1 knockout mouse model, all mice developed adenomas with high grade

dysplasia, and 30% went on to develop invasive carcinoma (48); III) TFF1 peptide showed a dose-dependent reduction in the proliferative activity of a human gastric carcinoma cell line without morphologic changes (49). Mutational analysis demonstrated a total 8 TFF1 somatic mutations, 5.5% of gastric adenoma and 16.3% of cancer cases, and the mutants showed loss of tumor suppressor activity and acquisition of invasiveness (50, 51). In addition, TFF1 expression was detected in only 16.7% of gastric adenoma, 38% of intestinal-type and 82% of diffuse-type gastric cancers. Since gastric adenoma and intestinal-type gastric cancer consisted mainly of cells with intestinal-type differentiation, this study provided compelling evidence that the TFF1 expression in gastric cancer simply disclose gastric-type differentiation of neoplastic cells (50).

3. Caudal Homeobox Gene CDX2

Cdx2 is a caudal homeobox gene which has been shown to play a role in the development of the small and large intestine in mammals, and in the differentiation of intestinal epithelial cells (52). Cdx2 stimulates differentiation by activating transcription of intestine-specific proteins, such as MUC2, sucrase, isomaltase, carbonic anhydrase I (53, 54), and up-regulating WAF1 (also known as p21), indicating that Cdx2 functions as a proliferation inhibitor and a differentiation inducer (55). Intestinal metaplasia of the stomach is characterized by transdifferentiation of gastric epithelial cells to an intestinal phenotype, accompanied by the expression of intestine-specific genes, including MUC2 sucrase, and carbonic anhydrase I (13). Cdx2 is not expressed in normal stomach, but is highly expressed in the normal intestine and in intestinal metaplasia of the stomach (56), suggesting that Cdx2 is involved in the induction of intestinal metaplasia. Although it is possible that H. pylori-associated chronic inflammation induces Cdx2 expression, it is still unclear how Cdx2 expression is triggered in stomach. Cdx2 plays a critical role in tumor suppression through its ability to transactivate p21 cdk inhibitor transcription. The intestinal metaplastic mucosa of Cdx2-transgenic mice caused intestinal-type adenocarcinoma in the stomach with a 100% cancer incidence (56, 57). In our previous report, we found allelic loss at the Cdx2 locus in 25% of cases, somatic missense mutations in 2 (2.1%) intestinal-type gastric cancers, loss of expression of Cdx2 protein in cases with mutations and allelic loss (58). Therefore, ectopic expression is one of the contributing factors of intestinal metaplasia, and defective Cdx2 expression by genetic alteration accelerates the transformation of metaplastic cells to gastric cancer.

4. p53

The p53 gene is located in chromosome 17p13.1, and is the most common target for genetic alteration in human tumors, including gastric cancer. p53 is a transcriptional factor at the center of various signals mediating DNA damage, hypoxia, cell-cycle arrest, senescence and apoptosis. The p53 protein functions as a critical gatekeeper against cancer formation and plays an important role in cell growth and division (59). In cells with inactivating p53 mutations, DNA damage does not induce cell cycle arrest or DNA repair; mutations accumulate in dividing cells and genetically damaged cells proliferate, giving rise to cancer (59). Somatic mutations of p53 have been identified in approximately 30% to 50% of gastric cancers (60, 61). The frequencies of p53 mutation in early and advanced differentiated gastric carcinomas

are found consistently in approximately 40% of each disease state, and are similar to that observed in advanced undifferentiated carcinomas (62, 63). However, p53 mutations are rare in early undifferentiated carcinomas, indicating that frequent p53 mutations in advanced undifferentiated carcinoma can be postulated to be due to frequent conversion of differentiated cancers to undifferentiated phenotype as the tumor progresses (64).

p53 mutations also occur in gastric adenomas. Interestingly, the mutations tend to be silent in gastric adenoma with mild or moderate dysplasia, but missense mutations have been identified in with high-grade dysplasia, suggesting that p53 missense mutations is a key indicator of malignant transformation (65, 66). When we searched for p53 mutations in 50 gastric adenomas of size less than 2 cm, and 90 malignant gastric specimens after microdissection under light microscope, mutations were detected in 14% of gastric cancer, but not in adenoma (unpublished data). Although it is possible that discrepancy in the frequency of p53 mutations depends on the mutational screening methods used, sample size and tissue fixatives, it remains likely that p53 mutations contribute to the development of Korean gastric cancer, but not protruded adenoma less than 2 cm.

5. Wnt Signaling Pathways

β-catenin is a multifunctional protein that plays an important role in the transduction of Wnt signals and in intercellular adhesion by linking the cytoplasmic domain of cadherin (67). In general, the cytoplasmic level of β-catenin is kept low through interaction with a protein complex comprised of adenomatous polyposis coli (APC), Axin, protein phosphatase 2A and glycogen synthase kinase 3β. Therefore, alterations of these genes cause accumulation of cytoplamic β-catenin and nuclear translocation of β-catenin. After its translocation into the nucleus, stabilized β-catenin binds to members of the Tcf/Lef family, thereby activating target genes such as cyclin D1 and myc. It has been repeatedly reported that mutations of the Wnt signaling pathway related genes are involved in human cancer development and/or progression (68). Of these, inactivation of the APC gene during early adenoma formation is thought to be the first genetic event in colorectal carcinogenesis, followed by K-ras and p53 gene mutations (69). In the stomach, somatic APC missense mutations have been reported in Japanese gastric adenomas and adenocarcinomas (70, 71). However, other reports, including Japanese patients, have not identified significant APC mutations in gastric adenoma and adenocarcinomas (72, 73). Since the long arm of chromosome 5, in which the APC gene resides, is commonly deleted in gastric adenocarcinomas (74), it is likely that a new candidate tumor suppressor gene(s) exists in this region.

Most β-catenin mutations are activating mutations, mainly occurring at one of four phosphorylation sites in exon 3 (68, 75), and aberrant cytoplasmic overexpression or nuclear accumulation of β-catenin is frequently found in sporadic gastric cancers (76). Interestingly, β-catenin mutations were found in intestinal-type gastric cancers, but not in the diffuse-type, and decreased normal membranous expression of β-catenin was associated with poor differentiation and poorer patient survival (75, 77, 78). Although β-catenin mutations were not present in both intestinal and foveolar types gastric adenomas, the frequencies of genetic alterations, including APC, K-ras and MSI occurring in gastric adenomas were similar to colorectal adenomas (79).

Recently, somatic mutations of β-catenin, Siah-1, β-TRCP, and Pin1 genes have been found in Korean gastric cancers patients (75, 80~82). In functional analysis, mutants Siah-1 detected in gastric cancer stabilized the cytoplasmic levels of β-catenin and failed to suppress cyclin D1 expression and induce apoptosis, suggesting that constitutive activation of Wnt canonical pathway contributes to gastric carcinogenesis (80). Since only one of these genes is mutated in a given tumor sample reflecting their role in a common pathway (83), further studies are necessary to elicit other mechanisms activating Wnt signaling pathway implicated in the development of Korean sporadic gastric cancers.

6. Microsatellite Instability

In addition to genetic and epigenetic alterations affecting oncogenes and tumor suppressor genes, genomic instability also play an important role in carcinogenesis. Two major genomic instability pathways, microsatellite instability (MSI) and chromosome instability (CIN), are involved in gastric carcinogenesis. Microsatellites are tandem repeats of one to six nucleotides found throughout the genome and MSI is defined as increase or decrease in length of these microsatellites in tumor cells by replication errors. CIN has been linked to aneuploidy and chromosomal aberrations, either qualitative or quantitative. Despite the fact that CIN has been considered a hallmark of cancer and a common pathogenic process in gastric cancer, the exact molecular mechanism of CIN remains to be fully elucidated. Knowledge on MSI patterns in gastric cancer is summarized in this review. MSI phenotype was first characterized in HNPCC or Lynch syndrome (84). In contrast to colorectal cancer, mutations of the DNA mismatch repair genes, MSH2 and MLH1, are rare and hypermethylation of MLH1 promoter CpG island was found to be responsible for MSI-H gastric cancer development (85, 86). Three levels of MSI can be identified; high-frequency MSI (MSI-H), if 2 or more of the 5 microsatellite markers show instability, low-frequency MSI (MSI-L), if only 1 of the 5 markers shows instability, and microsatellite stable (MSS) in the absence of microsatellite alteration (87). By adopting these criteria, we reported a frequency of 14% MSI-H, 7% MSI-L and 79% MSS in a series of Korean gastric cancers (74). MSI has been found in sporadic gastric cancer ranging from 13% to 44% of tumor samples (88). Gastric cancer with MSI-H identified a well-defined subset of gastric cancer characterized by unique clinicopatholgical features including intestinal-type, antral location, lower prevalence of lymph node metastases and relatively improved long-term survival compared to MSS/MSI-L counterparts (89). In addition, gastric carcinomas with MSI-H may also harbor frameshift mutations in the coding region of cancer related genes, such as BAX, IGFRII, TGFBRII, and hMSH3 (88,90). These mutational events inactivate only one of the two alleles of these genes, leading to haploinsufficiency. The accumulative haploinsufficiency model for cancer of the mutator pathway is not restricted to genes affecting cell growth or survival, but may also extend to genes involved in genome integrity, including the mismatch repair genes themselves, suggesting that these mutations drive cells to further progress in malignancy (91). Therefore, it has been proposed that MSI can be used as a marker for screening genetic instability and early diagnosis of gastric cancer.

MSI was also reported in 7~35% of gastric adenomas (92, 93). Although pathologic observations have

suggested that malignant transformation of gastric adenoma occurs in only 2.5% of conventional protruded and 5.0% of depressed adenomas (94), detection of certain genetic alterations including MSI in adenomas may be indicative of malignant transformation (95).

7. Apoptotic Pathway

Homeostasis in living organisms is achieved by maintaining a balance between cell survival and cell death signaling. Apoptosis is a pathway of cell death induced by a tightly regulated suicide program, in which cells are destined to die. Apoptotic cell death is an evolutionarily conserved process, occurs normally during development and serves to eliminate unwanted or potentially harmful cells. A defective apoptotic pathway may therefore contribute to cancer development, progression and treatment failure. Generally, apoptotic cell death occurs by two distinct pathways: the intrinsic pathway (also known as mitochondrial pathway) and the extrinsic pathway (also known death receptor-initiated pathway) (96). The mitochondrial pathway can be triggered by any stimuli, including growth factor withdrawal, oxidative stress and DNA damage. The key sensors in the mitochondrial pathway is the Bcl-2 family, which consists of more than 20 members of pro-apoptotic proteins, including Bax, Bak, Bad, Bid, Bim, Bcl-Xs, and Noxa, and anti-apoptotic proteins, including Bcl-2, Bcl-XL, Bcl-W, and Bcl-G (97, 98).

In contrast to the mitochondrial pathway, death receptor pathway is induced by death ligand binding to receptors. The death ligand-receptor system includes Fas lignad-Fas, tumor necrosis factor (TNF) - TNF receptor 1 (TNFR1), TRAIL-TRAILR1 (also known as DR4) and TRAIL-TRAIR2 (also known as DR5) (99,100). Binding of Fas ligand to Fas or TRAIL to TRAIL-R leads to recruitment of FADD (Fas-associated death domain), and binding of TNF to TNFR1 leads to recruitment of TRADD (TNFR-associated with death domain). These proteins form a complex, called DISC (death-inducing signaling complex) and trigger the caspase cascade and apoptotic event (101).

Gastric cancer development is a very complex process and anti-apoptosis is another possible mechanism that may be associated with gastric carcinogenesis. Any agent capable of inducing apoptotic cell death selectively in cancer cells will provide a powerful treatment strategy in gastric cancer patients. Although H. pylori induce apoptosis by increasing Bak expression in gastric tissues from patients infected with the bacteria and in vitro, H. pylori also induce anti-apoptosis through c-IAP2 transactivation flowing cagPAI-dependent NF-kappaB activation (102, 103). Procancer cells, defined as cancer clones that do not show distinguishable morphological atypia, but exhibits positive DNA-instability testing and positive staining for biomarkers such as Ki67, p53, and bFGF, are already present at the adenoma stages showing enhanced proliferative activity, p53 mutation, and enhanced survival by escaping apoptosis (104). Fas and FasL expressions were observed in 38% and 36% of gastric adenomas, respectively (105). However, somatic mutations in apoptosis related genes have not been reported in gastric adenomas. In gastric carcinogenesis, activating mutations of apoptosis-inducing gene or inactivating mutations of apoptosis-inhibiting genes that drive uncontrolled cell survival are also requisite events. Fas and Fas ligand are constitutively expressed in gastric cancer (106). In our previous study, missense mutations of the Fas gene were observed in 11.6% of gastric cancer samples,

without significant difference in the frequency of mutation between intestinal-and diffuse-type gastric cancers. Wild-type Fas induced high frequency of apoptotic cell death, but tumor derived mutant Fas significantly failed to induce apoptosis (107, 108). We also found DR5 missense mutations in 7% of gastric cancers and all the mutants inhibit apoptotic cell death. Interestingly, tumors containing the DR5 mutation did not carry p53 mutation (109). In addition, there are several reports describing infrequent somatic mutations of apoptosis related genes, including Bid and caspase 9&10, in gastric cancer (110~112). All of these data suggest that inactivation of apoptosis-inducing gene caused by somatic mutations may be one possible escaping mechanism against apoptotic cell death, and may contribute to the progression intestinal- and diffuse-types gastric cancer. It is therefore crucial to find out the molecular mechanisms of anti-apoptosis in gastric cancer cells, and to develop selective apoptosis inducing agents in cancer cells.

Conclusion

Most neoplasms arise from a single cell, and tumor progression results from acquired genetic variability within the original clone, allowing sequential selection of more aggressive sublines (113). Under this hypothesis, sequential genetic alterations have been extensively demonstrated in colorectal cancer (114). Finally, molecular genetic studies have yielded many insights into pathogenesis that drives carcinogenesis. However, only a small fraction of cancer (6.6%) have been shown to contain three most frequent mutations: APC, K-ras and p53 genes, suggesting that multiple genetic pathways exist, and that the widely accepted genetic model of cancer development is not representative of the majority of colorectal tumors (115). In my experience, each gastric cancer contains different genetic alterations in the process of tumor development and progression, suggesting that gastric cancer is a biologically and genetically heterogeneous disease, not only from tumor to tumor, but also within a tumor. The molecular pathways of gastric cancers are mainly dependent upon histologic differentiation and other molecular mechanisms, including chromosomal instability and epigenetic alterations. As such, there exist many challenges to overcome. In order to understand the exact molecular mechanisms, to identify early diagnostic markers and to develop more effective therapeutic strategies, further studies are crucial in unraveling molecular cancer genetics: how gastric cancer cells initiate, proliferate, invade, and metastasize. Genetic alterations described herein, and from as yet unidentified target genes in gastric cancer cells, will help to us guide towards more effective diagnosis and treatment. Translational studies of molecular genetics will provide us with novel diagnostic, prognostic and therapeutic modalities in gastric cancer.

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Peer Reviewers' Commentary

본 논문은 헬리코박터, TFF1, CDX2 등 최근 밝혀진 위암과 연관된 분자유전학적 요인들과 가족성 위암과 연관된 유전적 변이에 대해서 기술하고 있다. 논문에서 밝힌 대로 위암의 유전자 변이는 다양하고, 각각의 유전자 변이는 종양의 발생, 조직학적 특성, 종양의 침윤 및 전이 등과 연관되어 있으며 다른 유전자의 변이와도 밀접하게 연관되어 있다. 따라서 위암의 다양한 분자유전학적 변화를 이해하는 것은 학문적으로 중요할 뿐 아니라 이를 통해 위암 환자의 예방, 진단 및 치료 방법의 발전에 크게 기여할 수 있을 것이다. 그러나 위암과 연관된 분자유전학적 요인들을 환자의 진단 및 치료에 적용하기 위해서는 향후 추가적인 중개 연구와 연구 결과의 검증이 요구된다.

[정리 : 편집위원회]