Polymorphism

REVIEW

# Molecular aspects of gastric cancer development: a mini review

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ABSTRACT

Gastric cancer is still a common problem and is responsible for a large proportion of worldwide cancer mortality, linked to low survival rates. Gastric cancer is a complex, multifaceted process caused by a complicated interaction of environmental and genetic variables. Despite the fact that numerous studies have been conducted on genetic alterations that lead to its genesis, the exact causes remain unknown. Gastric cancer is thought to be caused by various genetic or epigenetic changes, including microsatellite instability (MSI), tumor suppressor genes deactivation, and oncogene overexpression. Apart from that, molecular determinants like cell-cycle regulators and cell adhesion molecules are also responsible for the progression of gastric malignancies. Identifying the etiology of gastric cancer through molecular genetic alterations may assist in the creation of new biomarkers for vulnerability assessment, diagnostic, prognostic, and therapeutic approaches. This review summarizes our current understanding of the molecular basis of gastric cancer, including numerous molecular changes in its pathophysiology and tumorigenesis.

KEYWORDS: Gastric cancer, genomic mechanisms, oncogenes, tumor suppressor genes

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## INTRODUCTION

Gastric cancer is still the second biggest reason of death worldwide among all cancers. Although death rates have been decreasing, most patients who develop GC are aged 65 to 74. The disease affects men twice as often as women. African Americans, Spanish Americans, and Native Americans are more likely to develop GC than white Americans(Koh and Wang 2001). In Indian subcontinent, the rate of gastric cancer in the north-eastern areas are greater than the rest of the country. According to studies, the rate of gastric cancer in the urban regions are 3.0–13.2 when compared to global rate (4.1–95.5), and these are high among males (50.6) than females (23.3)(Dikshit et al. 2011; Sharma and Radhakrishnan 2011). According to Cancer Statistics, 2020, gastric cancer is projected among five most common cancers in 2020 for males, which accounts for 36% out of all cancers(Mathur et al. 2020).

Gastric cancer is a complex, multifaceted phenomenon caused by a complicated interaction of environmental and genetic variables. Apart from genetic factors, the non-genetic determinants of gastric cancer consist of poor dietary habits, *H. pylori* infection, family history, and tobacco smoking(Fujino et al. 2002; Lazarevic et al. 2010). Diet has a significant influence in the development of gastric cancer. High salt intake has been linked to an increase in gastric cancer morbidity and death. High-salt foods may harm the stomach mucosa, resulting in gastritis, excessive DNA synthesis, and increased cell replication. Chronic salt consumption may exacerbate *H. pylori*-related carcinogenesis by promoting *H. pylori* proliferation, colonisation, and mucosal atrophy(Furihata, Ohta, and Katsuyama 1996; X.-Q. Wang, Terry, and Yan 2009). For decades, researchers have been aware of the impact that alcohol intake plays a crucial role in carcinogenesis. The ethanol in alcoholic beverages causes oxidative stress, which damages DNA and impairs its repair. Acetaldehyde is the first metabolite generated during alcohol breakdown and it may have a more prominent role in the carcinogenic effect of ethanol on the mucosa because of its numerous mutagenic effects on DNA(Baan et al. 2007; Salaspuro 2011).

Obesity is another major concern, which raises the risk of gastric malignancies. Obesity is thought to be responsible for 14% of all cancer deaths in men and 20% in women(Calle et al. 2003). Obesity-related gastro-oesophageal reflux, insulin resistance, abnormal levels of adiponectin, leptin, and ghrelin, as well as an unusually high blood level of insulin-like growth factor, are all possible pathways connecting obesity to gastric cancer(Li et al. 2012; Donohoe et al. 2014; Karczewski et al. 2019). The gut microbiome/ microbiota are varied population of bacteria that lives in the human gut. Human gut bacteria are also thought to have a key role in the genesis of gastric malignancies, particularly by dysbiosis (imbalance in the gut microbiota, which can contribute to a variety of clinical disorders, especially GC)(Thursby and Juge 2017). The entire research till date on the gastric microbiota performed shows that the microbiota changes as the gastric mucosa progresses from normal to cancerous. But, these studies have shown conflicting results when it comes to whether the microbiota of stomach cancer patients has more or less variety than the microbiota of healthy people; therefore, there is a scarcity of evidence on the relationship between the gut microbiota and GC occurance(Bik et al. 2006; Dicksved et al. 2009; Aviles-Jimenez et al. 2014; L. Wang et al. 2016; Stewart, Wu, and Chen 2020).

However, the exact process of GC formation is yet unknown. Metabolic pathway metabolites play a critical role in controlling cell differentiation during carcinogenesis as well as normal growth. A recent study shows that glutamine metabolism plays a crucial role in tumorigenesis because it is an excellent source of reduced nitrogen for the synthesis of purine and pyrimidine bases, as well as

proteins(Addeo et al. 2021; Ratre et al. 2021). Despite many advancements in the treatment strategies of GC, the tumor's resistance mechanisms provide a significant barrier to the development of successful cancer treatments. Recent data suggest that miRNAs have a critical role in tumor development and also cause chemoresistance in GC. The expression of certain kinds of microRNAs is increased in GC. Thus it has potential diagnostic values in the prediction of the disease(Verma et al. 2020; Verma and Bhaskar 2020). Although there has been significant improvement in the diagnostic and therapeutic approach, the life expectancy remains static and low, with approximately 20% of individuals with GC surviving for five years(Singh et al., n.d.). Due to this, a comprehensive understanding of the genetic basis of GC is required to develop innovative GC preventive and treatment techniques. The objective of this review is to emphasize the pathophysiology of the most common forms of gastric cancer.

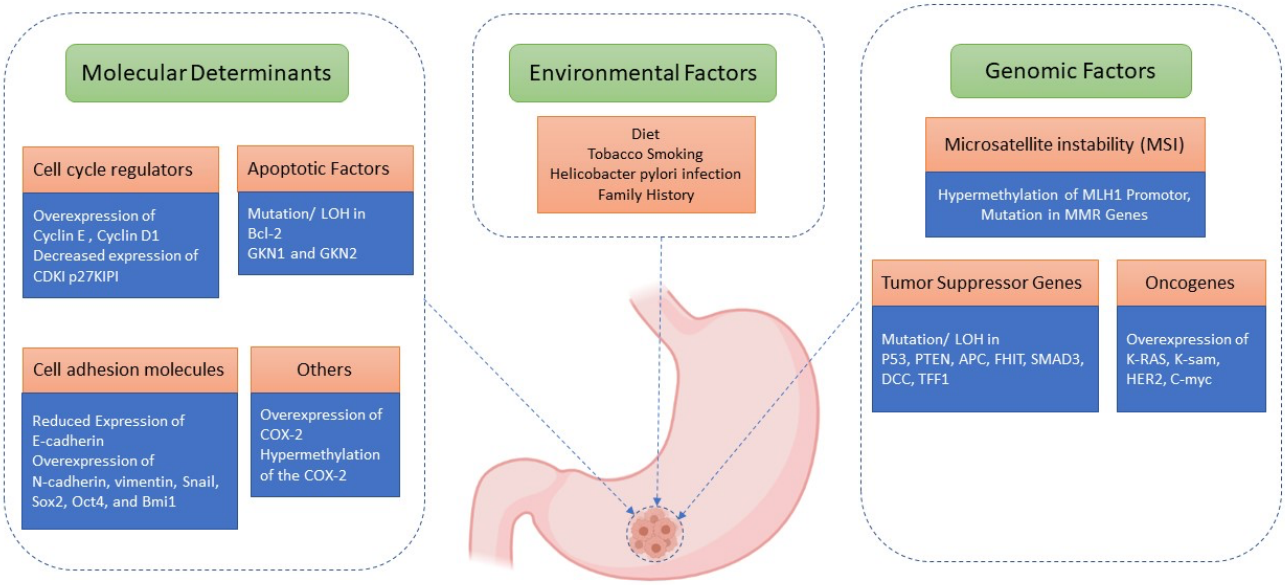


Fig. 1. Factors that cause the development of gastric cancer

Gastric carcinoma, which comprises of more than 50% of all gastric cancers, is classified into two subgroups by Laurens's classification: intestinal and diffuse(LAUREN 1965). The intestinal form is defined by cancerous epithelial cells with cohesion and glandular development that infiltrate the surrounding regions. It is linked with *H. pylori* infection, overweight, and other dietetic aspects like a huge salt consumption, smoked meats, and various food preservatives. The diffuse category is defined by cancer cells with low development and non- cohesiveness. It is also known to be developed by *H. pylori* infection with chronic inflammation(Cristescu et al. 2015; Crew and Neugut 2006). Factors that cause the development of gastric cancer are depicted in Figure 1.

## Genomic mechanisms of gastric carcinogenesis

Although gastric cancer's genomic mechanisms are complex and poorly understood, rapid developments in cancer biology have shown that converting a normal epithelial cell into a cancerous cell is a sequential process involving the collection of numerous genetic alterations (Chan et al. 1999; Correa 1992; Powell et al. 1992). Gastric cancer is thought to be caused by multiple genetic and epigenetic changes, as genomic instability is an essential discovery in gastric cancer(Hanahan and

Weinberg 2000). Many molecular anomalies/ genomic instability were documented, including microsatellite instability (MSI), deactivation of tumor suppressor genes, and overexpression of oncogenes(Correa 1992; Werner et al. 2001; Meining et al. 2001).

## Microsatellie instability (MSI)

MSI is associated with replication errors in microsatellite sequences due to a deficiency in the mismatch repair system. A set of mismatch repair (MMR) proteins detects and corrects these errors. MSI is caused by the deactivation or lack of MMR genes, typically MLH1 or MSH2, which often cause other genetic alterations, such as down-regulation of the tumor suppressor genes(Hudler 2012; Buermeyer et al. 1999). In MSI, the number of microsatellite repeats in tumor cells is different from normal cells. MSI is among the early changes in tumorigenesis that lead to genomic instability(Miyoshi et al. 2001). Rather than searching for a specific gene, the MSI method can be utilized as a screening tool for early cancer detection. CpG island methylator pathway defines the methylation in gastric cancer. Hypermethylation in the hMLH1 gene is linked with functional inactivation or silencing of the gene. Epigenetic hypermethylation of the MLH1 promoter has been associated with the formation of more than half of MSI-H-positive gastric malignancies.

In contrast, alterations in MLH1 and MSH2 have been detected in 12 to 15 percent of MSI-H-positive gastric carcinomas(Toyota et al. 1999; Leung et al. 1999; Hudler et al. 2004; Etoh et al. 2004). BCL2 associated X gene, MutS homolog 3 and 6, E2F Transcription Factor 4, TGFRII, insulin-like growth factor receptor II, TCF 4, RIZ, CASPASE 5, FAS, BCL10, and APAF1 were reported to be mutated in gastric cancers with MSI. These genes have been linked to the control of cell-cycle transition and apoptosis(Fiocca et al. 2001; El-Rifai and Powell 2002; Ottini et al. 2006).

## Tumor suprressor genes

Tumor suppressor genes prevent cells from turning malignant by repairing DNA, which inhibits cell growth and triggers apoptosis. Tumor suppressor genes have functions in various cell activities such as cell adhesion, cell interaction, cytoplasmic signaling processes, and nuclear transcription. Tumor suppressor gene inactivation because of mutations and/or loss of heterozygosity (LOH) is another common occurrence in gastric carcinogenesis. Mutation or loss of function of the p53 gene was observed in 80% of gastric carcinomas (Werner et al. 2001; Shiao et al. 1994), and changes in the p53s function caused by LOH include a high frequency of p53 alterations and DNA methylation in rare cases (Verma, Falco, and Bhaskar 2020). The p53 gene is known to be the primary regulator of cell division. p53's biological purpose is to protect genomic integrity, and cells that lack normal p53 function will not initiate apoptosis and hence do not control the growth of tumors(Vousden and Prives 2005). Over 50% of malignancies, comprising leukemia, breast, colon, and lung carcinoma, have abnormal p53 expression, and p53 mutation perhaps has the highest prevalence in all of them. p53 is a crucial player in the cell cycle; after DNA damage, p53 inhibits the G1/S shift, thus enabling DNA repair and apoptosis. LOH of the chromosome 17p, which codes p53, is seen in 62% of the atypical intestinal forms of GCs developed by gastric carcinoma(H. S. Kim et al. 2001). PTEN is another tumor suppressor gene that was discovered in 1977. It controls multiplication, apoptosis, motility, adherence, and genomic integrity through a sophisticated network structure that governs a range of cellular activities and signaling pathways. It is a lipid phosphatase that inhibits the PI3K signaling pathway by obstructing PIP3 dependent processes like activation of AKT(Xi and Chen 2015). So, upon the loss of expression of PTEN, the PIP3 level will be increased, which also increases AKT activation, which ultimately inhibits apoptosis(Xu, Yang, and Lu 2014). PTEN protein expression is substantially lower

in gastric cancer in contrast to normal. Genes of phosphatidylinositol 3-kinases, Protein kinase B, Matrix Metallopeptidase 2 and 9, and nuclear factor-B (NF-Bp65) protein are, on the other hand, overexpressed in GC(Wen et al. 2010). Alterations or LOH of the APC (tumor suppressor gene) are also found in sixty percent of intestinal-form of gastric tumors and approximately twenty five percent of adenomas(Horii et al. 1992; Wright and Williams 1993; Tahara 1995). According to a recent study, somatic mutation of the APC gene has a significant role in the etiology of benign gastric tumors, but only a minor impact in its development to malignant carcinoma(J.-H. Lee et al. 2002).

Further, the APC protein plays a vital role in the degradation of β-catenin, a transcription factor of the Wnt signaling pathway(Hsieh and Huang 1995; Caca et al. 1999; Park et al. 1999). APC protein binds specifically to β-catenin, and after combining with transcription factor LEF-1, β -catenin move into the nucleus, at which it controls gene expression. Mutation in β-catenin/lymphoid-enhancing factor have been discovered in intestinal-type of GC (Park et al. 1999; Peifer 1999). In patients with familial adenomatous polyposis (FAP), where 60–80 % of APC genes are mutated, there is also evidence of a link between APC and gastric cancer (Kinzler et al. 1991; Lynch and Lynch 1998), and individuals with FAP have ten times increased lifetime risk of gastric cancer than ordinary people(Zwick et al. 1997). APC is also altered by extensive methylation and leads to premalignant stages leading to gastric cancer. Methylation in APC has been found in greater than 75% of the intestinal forms of GC(Esteller et al. 2000; Sarbia et al. 2004). p16 is a CDK inhibitor that arrests the cell cycle at the G1 phase, and the reduced expression of p16 is seen in many intestinal GCs. This reduced expression of p16 is due to hypermethylation(Sarbia et al. 2004). FHIT is another tumor suppressor gene from FRA3B at the 3p14.2 site, which was abnormally expressed due to genetic alterations in most gastric cancers(Baffa et al. 1998; Ohta et al. 1996). SMAD3 is another tumor suppressor whose absence is linked to a severe phase and a worse prognosis in individuals with gastric cancer. It is more prevalent in the intestinal form than that in the diffuse form. DCC is a type of tumor suppressor gene located on chromosome 18q. One study found reduced mRNA expression of DCC in 52 cases of gastric malignancies and stated that the reduced expression was strictly related to liver metastasis(Yoshida et al. 1998). Trefoil factor family 1 (TFF1) is a gene found on chromosome 21q22, and its synthesis occurs in the stomach mucosa and gastrointestinal cells of injured tissue. This gene is also found deleted in most gastric cancers in LOH studies, and in some cases, its altered expression due to mutation is also seen(Bossenmeyer-Pourié et al. 2002; Park et al. 2000).

## Oncogenes

An oncogene is a mutated gene responsible for cancer progression, and these genes are expressed at high levels in cancer cells. RAS are oncogenes that are not found in regular cells but are triggered in cancer cells due to massive mutations that occur throughout tumor growth. K-ras is a cellular signaling protein that plays a significant role in developing pancreatic and colon cancers(Pellegata et al. 1992; Soh et al. 1993). K-sam, a member of the FGFR, is also shown to be overexpressed in diffuse-forms of gastric tumors(Katoh 2003). The c-erbB-2 OR HER-2/neu is a TKI receptor-like EGFR 2, HER2, and EGFR or HER1, and it is also overexpressed in all types of GCs(García et al. 2003). In intestinal-type GC, serum c-erbB-2 levels are considerably elevated in comparison with diffuse GC(Vizoso et al. 2004). The majority of research on this protein has found that HER-2/neu status has a substantial predictive value, and HER-2/neu overexpression was identified as a possible biomarker of prognosis in gastric malignancies(Mizutani et al. 1993; Allgayer et al. 2000; Y.-L. Wang et al. 2002). C-myc is an oncogene found on chromosome 8 that expresses a nuclear phosphoprotein that functions as a transcription factor (TF) by stimulating and inhibiting the expression of target genes. It also

involves regulating many genes responsible for critical cellular processes such as multiplication, development, differentiation, angiogenesis, DNA repair, and cell death. If myc gene is unregulated, it can lead to tumor development (Battey et al. 1983). C-myc overexpression is observed in more than 40 percent of gastric cancers. This is an initial phase in the development of both intestinal as well as diffuse gastric cancers. However, it is significantly more prevalent in the intestinal form as compared to the diffuse form. The C-myc gene has been reported to be highly expressed in benign forms such as chronic atrophic gastritis, gastric ulcer, and *H. pylori* infection(Calcagno et al. 2008; Dang et al. 2006).

## Molecular determinants of gastric cancer

### Cell cycle regulators and apoptosis

Cell cycle regulators such as cyclin proteins control the cell cycle by checkpoints by attaching and triggering particular cyclin-dependent kinases. G1-S phase progression is controlled via cyclin D, E, and A, and its kinases like CDK 2,4, and 6, whereas G2/M shift is controlled via B-type cyclin-associated kinase. Cell-cycle regulator abnormalities have also been associated with gastric cancer formation and development through uncontrolled cell growth(Yasui et al. 2001). Overexpression of cyclin E was associated with later cancer stage and metastatic spread in 10% of diffuse-form gastric cancers and 20% of intestinal-form gastric cancers(Yasui et al. 1997). Moreover, overexpression of cyclin D1 was identified in about 50% of gastric carcinomas, with the intestinal form being more common than the diffuse form(Müller et al. 1999), and the reduced expression of CDKI p27KIPI in GC is usually linked to the degree of tumor progression and the occurrence of lymph node metastasis(Yasui et al. 1997).

Apoptosis, or programmed cell death, plays a vital role in regulating a cell's entity. FAS, TNF, and bcl-2, are apoptosis-regulating genes that play a role in cancer development. Bcl-2 was discovered in a human leukemia line at the chromosomal breakpoint t (14;18) (Tsujimoto et al. 1984; 1985). Around fifteen Bcl-2 family member proteins in mammalian cells contained proteins that trigger and inhibit apoptosis (Gross, McDonnell, and Korsmeyer 1999). Although LOH at the bcl-2 region has been linked with intestinal-form of gastric carcinoma, the expression of an apoptotic receptor antigen identified by SC-1 antibody is predominantly found in diffuse-form of cancers(Werner et al. 2001; Vollmers et al. 1997; Klein, Vollmers, and MullerHermelink 1996). GKN1 has been found to block the G2/M cell cycle, inhibiting tumor cell development and lowering the number of cell colonies (Yan et al. 2011). In vitro studies revealed that both GKN1 and GKN2 had been found in the gastric mucosal lining of healthy people and the gastric mucosa of patients with GC; however, there is a contrast to those by superficial gastritis reduction in GKN1 mRNA expression and protein (Yoshihara et al. 2006; Oien et al. 2004; X.-Y. Guo et al. 2014; Zhang et al. 2010; Yan et al. 2011).

### Cell adhesion molecules

Gastric cancer also appears to be linked to changes in adhesion molecules. Cadherins like E, N, P, R, and M are predominant, with their names derived from the type of cell in which expression was initially identified (Shimada et al. 2012). E-cadherin is a β-catenin binding partner that is important for intercellular adhesion and epithelial tissue structural integrity. E-cadherin is a member of the cadherin superfamily and is engaged in epithelial phenotype maintenance. E-cadherin expression is often diminished or lost in gastric malignancies, most likely due to hypermethylation of the E-cadherin promoter(Tamura et al. 2000; Mingchao et al. 2001). Somatic changes in E-cadherin were found in 50% of patients with diffuse-form of gastric malignancy. In contrast, deletion of the leftover alleles, leading to full protein deactivation, was reported in more than 75% of cases with mutation(Becker et al. 1994; Oda et al. 1994). Oxygen deprivation is a strong activator of GC EMT (epithelial-mesenchymal transition). E-cadherin levels drop in hypoxic

conditions while N-cadherin, vimentin, Snail, Sox2, Oct4, and Bmi1 levels rise, suggesting that the hypoxia promotes epithelial-mesenchymal transition and cytoskeleton remodeling(J. Guo et al. 2016).

### Cyclooxygenase (COX)-2

Nonsteroidal anti-inflammatory medications block COX-2, the primary enzyme involved in converting arachidonic acid to proteinoids. COX-2 overexpression has been related to inflammatory processes and carcinogenesis in various human malignancies, most notably colorectal, esophageal, and gastric cancers(B P van Rees and Ristimäki 2001; Rajnakova et al. 2001; Bastiaan P van Rees et al. 2002). Overexpression of COX-2 is typical in the intestinal form of gastric cancer, and dysplastic precursor lesions, representing that COX-2 expression is involved in gastric carcinogenesis at an early stage(Lim et al. 2000; Saukkonen et al. 2001). Furthermore, in gastric cancer, COX-2 overexpression is significantly and inversely associated with MSI(T. L. Lee et al. 2001). Hypermethylation of the COX-2 CpG island in gastric cancer cell lines has been demonstrated to produce COX-2 transcriptional suppression. Furthermore, COX-2 expression in gastric epithelial cells is controlled by *H. pylori*-stimulated promoter methylation(H. Kim, Lim, and Kim 2001; Song et al. 2001).

## CONCLUSION

Several important discoveries about the molecular pathogenesis of GC have been made since the last decade. These findings may enhance our knowledge of molecular interactions involved in gastric carcinogenesis and ultimately, lead to the discovery of novel treatment regimens that precisely target genetic alterations for this common disease. The characterization of GC at the molecular and genetic level supports the idea that this disease is very divergent. As evidenced by the complexity and variety of gastric tumors, gastric cancer is the result of a cascade of events involving diverse genetic and epigenetic alterations in multiple genes in combination with the host's genetic lineage and external conditions. Further research and meta-analyses are required to develop panels of biomarkers for assessment of vulnerability, diagnostic, prognostic, and therapeutic strategy.

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## Author's contribution

TS designed, planned, reviewed and prepared the manuscript.

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