Progress of Research in Gastric Cancer

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Gastric cancer (GC) has continued to be a threat to human life. Diagnosis of GC at advanced stage is considered as a major reason for lower overall five-year survival rate in developing countries. A complex set of molecular irregularities occurs at cellular level during early stage of GC and its further progression will disturb normal cell functioning. These abnormalities include genetic and epigenetic modifications leading to differential expression of many genes in normal and affected cells. Many efforts are made to spot these molecular aberrations to understand the underlying mechanism which governs abnormal cell behavior. Current review summarizes recent works addressing GC etiology, epidemiology, pathology and therapy treatment.

Keywords: Gastric Cancer (GC), Helicobacter Pylori, Polymorphism, Genetics, Epigenetics, Stem Cells.

CONTENTS
1. Introduction .................................................. 1
2. Risk Factors .................................................. 1
   2.1. Bacterial Infection ...................................... 2
   2.2. Smoking .................................................. 2
   2.3. Dietary Habits ............................................ 2
   2.4. Polymorphism ............................................. 2
3. Genetic Aberrations ........................................ 3
4. Epigenetic Changes in GC ................................... 4
5. GC Stem Cells ................................................ 4
6. Clinical Implications ....................................... 5
7. Conclusion and Perspectives .............................. 5
Acknowledgment ............................................... 5
References and Notes .......................................... 5

1. INTRODUCTION

Gastric cancer (GC) is the fourth common1,2 and second major cause of cancer deaths worldwide.2 Every year about one million new GC cases are reported, accounting for 8% of all cancer cases.3,4 The proportion of GC incidence is region specific. South America, Eastern Europe and especially East Asian countries5 are the most suffered regions. Noncardia GC cases have been considerably declined in North America6 and Western Europe during past few decades,7,8 but number of cardia GC cases are rising in American males.8,9 Beside it, GC incidence has been observed to be age and sex specific. Male to female noncardia GC incidence ratio is 1.5:1, whereas, cardia gastric ratio is 6:1.2 People whose age ranged between 50–60 years are more prone to this disease.9 Noncardia GC is more common in blacks and low socio-economic groups. Contrary cardia GC is more incident in whites and professional class.5

2. RISK FACTORS

Many external and internal factors influence the development of GC. These factors have been discussed in details in the following sections.

2.1. Bacterial Infection

Many studies have been conducted to identify possible causes that may contribute to the development of GC. Helicobacter pylori infection is implicated as a prime environmental risk factor for GC. Cytotoxin-associated gene A (Cag A) encoded in the PAI region, a pathogenicity island, of Helicobacter has been found virulent.4,10 It modifies the cellular signal pathways by interacting with Src homology 2 domain-containing protein-tyrosine phosphatase (SHP-2) in the gastric epithelial cells.6,8–13 Cag A protein carry EPIYA-A, -B, -C or -D motifs in the carboxyl terminus of protein.13 Bacteria containing Cag A EPIYA-ABD or multiple EPIYA-C motifs are more pathogenic strains.8,13 The difference in the Cag A motifs has found its basis in phylogenetic data. European and East Asian strains8 of Helicobacter pylori contain these specific
motifs and hence are more virulent.\textsuperscript{14} Cag A positive Helicobacter strains are more pathogenic than Cag A negative strains.\textsuperscript{9}

2.2. Smoking

Smoking has profound effects on GC occurrence. It manifests the risk of GC development.\textsuperscript{15-17} Cigarette smoking manifests its effects through cyclooxygenase (COX) and its derived prostanoids, mainly including prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), thromboxane A\textsubscript{2} (TXA\textsubscript{2}) and prostacyclin (PGI\textsubscript{2}).\textsuperscript{18} Nicotine and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are the most dangerous components in the cigarette smoke which promote cell proliferation, invasion and suppressed apoptosis.\textsuperscript{14} Nicotine promotes tumor growth and mediates gastric cell metastasis through COX-2/prostaglandin E\textsubscript{2},\textsuperscript{15} alpha 7 nicotinic acetylcholine receptor (alpha 7-nAChR)\textsuperscript{20} and Nicotine activated 5-lipoxygenase (5-LOX),\textsuperscript{21} resulting in downregulation of E-cadherin and upregulation of ZEB-1 and snail. Suppression of E-cadherin is a level-one hallmark of the epithelial to mesenchymal transition.\textsuperscript{29}

2.3. Dietary Habits

Dietary habits largely determine the chances of GC occurrence. Meta-analysis of habitual salt intake studies revealed that consumption level of salt was directly proportional to the increasing risk of GC.\textsuperscript{22} High intake of nitrate as well as nitrate from animal sources doubles the GC risk. On the other hand, use of polyphenols such as cinamic acid, secoisolariciresinol and coumestrol from plant sources reduces GC risk through inhibition of endogenous nitrosation.\textsuperscript{22} High consumption of red and processed meat is associated with GC.\textsuperscript{24,25} Other dietary components such as fruits, vitamin C, some carotenoids and high intake of dietary fiber are negatively associated with the GC.\textsuperscript{24,27} High alcohol intake may also increase the risk of GC.\textsuperscript{16,28,29}

2.4. Polymorphism

Development of GC not only depends on external factors but the susceptibility of the individuals to fall victim of this disease varies depending upon their genotypes.

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Approximately 10–15% of GC cases has familial history. Mutation and polymorphism in CDH1 gene, encoding E-cadherin, a molecule crucial in the maintenance of the epithelial architecture, is strongly associated with familial GC. CDH1−/− mice have been found to play an important role in cancer development. A allele carriers have significantly increased risk for GC among Caucasians. Contrary to this, a allele has protective role in Asians.

Genes involved in signaling receptors of *H. pylori* in gastric epithelial cells, activation of inflammatory responses, protection of gastric mucosa, Phases I and II metabolizing enzymes and DNA damage repair could be critical in GC. TLR2 −196 to −174 del and TLR4 +896G may increase the risk of GC. In another case study, TLR5 rs5744174 was linked with development of GC. Polymorphism of genes related to inflammatory response such as IL1B and IL1RN, TNF-α, LTA, COX2, HLA and other IL may affect susceptibility of an individual to GC. Meta analysis study suggested that IL1B −317C polymorphism played a protective role among asians whereas IL1B +51 T carriers were found to have an increased risk of cardiac GC specifically among Non-asians. IL1RN has also been implicated to increased GC risks confined to Non-Asian population. Recent meta-analysis suggested that IL−8 −251 AA genotype might be an important biomarker of GC susceptibility for Asians. There is a close connection between IL−10 −1082 gene polymorphisms and GC susceptibility among Asian and Caucasian populations. Carrying C allele in the Mif −173 G/C promoter polymorphism has significantly greater risk for GC cancer development. COX-2 −1195G>A polymorphism has significant association with increased risk of digestive system cancers especially among Asian population. Genes belong to family of muin and trefoil functions to protect gastric mucosa. Alterations in these genes may hamper their protective role. In a recent study, T allele at the TFF1 −394 C/T polymorphism has been found as a risk factor for GC. Further research needs to be conducted for unequivocal conclusions. A meta-analysis of studies conducted in CYP1A1 polymorphism has revealed that it was not associated with GC risk. CYP2E1 metabolizes alcohol and dietary and tobacco-specific nitroamines. A meta-analysis advocated significant positive association for carriers of the variant allele c2 in Asian population. Stratified analysis according to control sources also showed positive association between GSTM1 null genotype and increased risk of GC among Asians. Studies in GSTP1 codon 105 polymorphism proposed its association with GC among Caucasians.

NQO1 C697T has been established to be significantly associated with risk of GC among both Europeans and Asians in a meta-analytical study. ERCC2 Lys751Gln and Asp312Asn polymorphisms may contribute to increased risk of GC among Asians. XRCC1 Arg194Trp homozygous mutant genotype (Trp/Trp) has found to be associated with increased risk of GC in Asians. XRCC3 241M allele may act as a GC risk factor in Asians, while the XRCC3 241 T allele may act as a GC risk factor in Caucasians.

Close relationship between polymorphisms having different types and stages of GC is evident. MMP7 −181 A>G and MMP2 −1306 C>T have been associated with increased and decreased cancer risk respectively. In MTHFR C677T polymorphism, allele T is associated with a 17.3% increased risk of GC in Asians. There is a significant association between EGFR SNP +61A/G and risk of most cancers. Ser31Arg polymorphism has significantly decreased risk for GC among Asians. PSCA rs2294008 C>T and rs297392 G>A polymorphisms may contribute to the GC risk both among Asians and Europeans. For tumor protein p53 (TP53) Arg7Pro, the Pro allele at codon 72 of TP53 acts as risk factor of GC among Asians, and this association is particularly pronounced in diffuse.

3. GENETIC ABERRATIONS

GC follows a complex set of events from its initiation to its development. Genetic changes underlying this process have been regarded as microsatellite instability (MSI) and loss of heterozygosity (LOH). The distinguished feature of MSI is the frame shift mutations in the mononucleotide repeats. It is more lethal if these mononucleotide repeats are present in the coding region or gene promoter site. LOH causes aneuploidy and it has more detrimental effects because of addition or deletion of gene doses which is less tolerated. LOH on chromosome no. 17 has been observed in many GC cases. MSI and LOH are main factors in determining what pathological pathway cancer will follow and help in distinguishing GC into sub-types.

Recent research on genetic alterations during course of GC has helped to understand tumor biology and identify previously unknown genes related to GC. ARIDIA, a member of the SWI-SNF family, alters chromatin structure and affects the transcription of many genes. It is frequently mutated in GC with High MSI. But an inverse relation is found between the mutations of ARIDIA and TP53. It was suggested that ARIDIA drives cancer development through epigenetic modification. In addition to ARIDIA, other genes encoding chromatin remodeling proteins (ARID1B, PBRM1, SMARCA1, CHD3, CHD4 and MBD2) and genes encoding histone-modifying proteins (SIRT1 AND SETD2) are also found mutated in GC. Mutation is detected in genes (CHD1, CHD2, CHD3, CHD4, CHD7, CHD8, and CHD9), involved in chromatin remodeling process in GC with Microsatellite Instability (MSI).

MicroRNA genetic regulation is an important mechanism of epigenetic regulation of Genes. Mutation in genes...
4. EPIGENETIC CHANGES IN GC

Epigenetic is an important mechanism for gene regulation. It acts through covalent and non-covalent histone modifications, methylation and demethylation of genes and micro RNAs. Specific chromatin-based mechanisms in the control of human INOS gene expression upon Helicobacter pylori exposure has been suggested.67 The chromatin changes at iNOS promoter include decreased H3K9 methylation and increased H3 acetylation and H3K4 methylation levels. Histone deacetylation has been observed to cause lower expression of RhoH gene in GC.68

DNA methylation is a process in which cytosine followed by guanine acquires a methyl group at position 5', which may lead to permanent silencing of genes. It has been widely noticed that number of tumor suppressor genes are methylated in GC and considered as one of the main phenotypes of GC.

Many tumor suppressor genes are down regulated under the mechanism of methylation during progression of GC. In a recent study, three new genes CHRNA3, DOK1 and GNMT were found hyper-methylated in GC.69 These genes are reported to be involved in neurotransmission and angiogenic growth, host response to infection, maintenance of methinine pool and methyl group supply respectively. Another important gene CPEB1 which codes for a cytoplasmic polyadenylation element (CPE) binding protein that controls the translational activation or repression of many proteins during development is hyper-methylated in GC.70 LMX1A is a critical regulator of cell-fate decisions using genetic fate and hyper-methylated in GC.71 TFPi2 (also known as IPS9 and MSPl) is a member of the Kunitz-type serine protease inhibitors, which negatively regulate the enzymatic activities of trypsin, plasmin and V1a-tissue factor complex, is inactivated in GC because of promoter hyper-methylation.72 Another study revealed that HSil-1 silencing occurred in GC through hyper-methylation mechanism and may function as a negative regulator of proliferation and invasion in GC by suppressing Wnt/b-catenin signaling at the cell surface.73 Carbone anhydrase (CA) IX is a member of zinc metalloenzymes and has been regulated by methylation mechanism in GC.74 Zinc finger transcription factors are involved broadly in development and tumorigenesis. Promoter hyper-methylation of ZNF331, ZNF382, and ZNF312b leads to gene silencing in GC.75-77

MicroRNAs are small non-coding RNA molecules which play very important role in post-transcriptional gene regulation. They control many important genes involved in diverse biological functions. Any change in expression of these RNAs adversely affects cellular mechanisms. miR-449 induces senescence and apoptosis by activating the p53 pathway and is down regulated in GC.78 MiR-486 targets OLFM4, which is an anti-apoptotic glycoprotein, and lowered expression of miR-486 in GC leads to enhanced cell proliferation.79 The expression of many other miRNAs is lost in GC that may be due to hyper-methylation of their promoter region. MiR-34b, miR-34c, miR9, miR-129 and miR212 are tumor suppressor genes and down-regulation of all these miRNAs have been recognized in GC by CpG island hyper-methylation.79-82

5. GC STEM CELLS

The discovery of stem cells in leukemia has opened new doors of research in cancer studies.83,84 Houghton et al., demonstrated that chronic infection of C57BL/6 mice with Helicobacter recruted bone marrow-derived cells in stomach and suggested their possible role in the development of GC.85 In GC, stem cells were isolated in 2009 by Takashi and co-workers.86 They used CD44 as a marker to inrity cancer stem cells in heterogeneous population of tumor cells. These stem like cells have shown resistance to conventional cancer therapy. Relapse of disease after successful treatment has been attributed to these cells and these cells are suggested to possess high metastatic potential.87, 88 It is thus proposed that eradication of these cells is very important for successful cancer treatment.

These facts have ushered an urgent demand to carry out research to provide an in depth knowledge of biology and functioning of these cells which comprise a small portion of tumor. An experimental study suggested that sonic hedgehog pathway is vital for stem like cells to maintain their identity in Gastric tumor.89 In that study, cyclophamine or SE1 was used to block SHH pathways and resulted in reduction of self-renewing capacity of tumorsphere cells than adherent cells. Cai et al. isolated cancer stem cells from human GC cell line, MKN-45. They blocked the Wnt pathway by DKK-1 which affected the self-renewing capacity of MKN-45 tumorsphere cells.90 Another study suggested that stem cell division is regulated by microRNA pathway,91 Golestan et al., revealed
in an experiment that miRNAs are differentially expressed in cancer stem cells and cancer cells. However they used only one human GC cell line, MKN-45, in their experiment. There is a need for conducting experiments including large number of gastric cell lines and primary cancer samples for more generalized results.

6. CLINICAL IMPLICATIONS

A number of molecular abnormalities occurred at cellular level during the progression of gastric tumor. Detailed knowledge and understanding of these abnormalities may help us identify markers for early diagnosis, prognosis of disease and accurate prescription of treatment and therapy at clinical level.

Early diagnosis of GC is very important to increase 5-year survival rate of GC patients. It delineates the availability of reliable bio-markers that help us recognize GC at early stages. Hyper-methylation of PAM5C, MYLK, RNF180, and SLC19A3 have been suggested as useful pre-warning biomarkers for GC. Vimentin methylation may serve as a useful marker for detection of tumor DNA in the serum of GC patients. Experiments have shown that hyper-methylation of PCDH10, MGMT, P16, RASSF2, RASSF1A, FLNC, CALCA, RARBeta, TIMP3, PAX5 and PAX6 have prognostic importance in GC.

Recent research in GC has pointed out many therapeutic targets. Down regulation of miR-331-3P and PCDH10 and up regulation of RPL6, EphA2 and YAP have been witnessed in different experiments as therapeutic targets for cancer therapy. Naphthazarin, S-adenosylmethionine, demethinib and gerinest were labeled as potential therapeutic agents. Further experiments should be conducted to verify above results before their clinical applications. Recently, nanotechnology has been developed much, its future development should promote the research in GC.

7. CONCLUSION AND PERSPECTIVES

Recent GC studies have enhanced our understanding of this disease. Yet there are many aspects to be unveiled. Abnormal expression of many genes underscores the importance of study models which encompass many genes and their interaction. Discovery of new biomarkers to identify cancer sub-types is necessary for personalized medicine. Currently our knowledge is very limited about the biology and nature of cancer stem like cells and their role in GC.

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References and Notes


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REVIEW

According to the page, it appears to be a citation page from a journal article. The page contains a list of references, each formatted with a number followed by the full citation details. The references include various authors and titles related to research in gastric cancer. For instance, one reference is to a paper by Singh et al. published in *J. Biomed. Nanotechnology* in 2011. Each reference is a hyperlink that can be clicked to access the full article. The page also includes the journal's title, *J. Nanosci. Nanotechnol.*, and various other references that seem to be related to the field of nanotechnology in biomedical applications.