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Review Article

Genetics and gastric cancer susceptibility

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Abstract: Gastric cancer has high morbidity and mortality in China. It is ranked first in malignant tumors of the digestive system. Its etiology and pathogenesis are still unclear, but they may be associated with a variety of factors. Genetic susceptibility genes have become a research hotspot in China. Elucidating the genetic mechanisms of gastric cancer can facilitate achieving individualized prevention and developing more effective methods to reduce clinical adverse consequences, which has important clinical significance. Genetic susceptibility results from the influence of genetic factors or specific genetic defects that endow an individual's offspring with certain physiological and metabolic features that are prone to certain diseases. Currently, studies on the genetic susceptibility genes of gastric cancer have become a hotspot. The purpose is to screen for the etiology of gastric cancer, search for gene therapy methods, and ultimately provide a scientific basis for the prevention and control of gastric cancer. This article reviews the current progress of studies on genetic susceptibility genes for gastric cancer.

Keywords: Gastric cancer, genetics, susceptibility

Introduction

Gastric cancer is a common digestive system tumor in China, where it is ranked number one in mortality due to malignant tumors [1, 2]. Currently, it is known that the development of gastric cancer is associated with underlying gastric diseases (such as gastritis, gastrectomy, etc.) [3], *Helicobacter pylori* (*H. pylori*) infection [4], and genetic susceptibility factors [4, 5]. Previous studies have shown that the development of 35%-60% of gastric cancers is associated with *H. pylori* infection [6, 7]; however, only some people with *H. pylori* infection develop gastric cancer. Therefore, genetic factors may also be important for the development of gastric cancer [4, 5]. The familial clustering phenomenon of gastric cancer and the fact that only a minority of people are affected after exposure to the same environment indicate that the genetic susceptibility of individuals to environmental exposure factors also plays an important role in the developmental of gastric cancer [8, 9]. Similarly, the results of epidemiological studies in recent years have also shown that only a minority of people who live in environments with a high incidence of gastric cancer are affected, suggesting that whether an individual develops gastric cancer largely depends on that individual's genetic susceptibility. In the presents study, we aimed to summary the relation between genetic polymorphisms and gastric cancer susceptibility.

Immune response-related genes

Genes that are related to the immune response mainly include interleukin (IL) genes, human leukocyte antigen (HLA) genes, and tumor necrosis factor (TNF) genes. There have been several studies on ILs in recent years [10-13]. For example, gene polymorphisms at many loci in IL-1 [11], IL-6 [10], IL-8 [12], and IL-10 [13] can increase the risk of developing gastric cancer. IL-1 is an important cytokine in infection and in amplifying immune responses, and it is also a potent inhibitor of gastric acid secretion. Its gene is located on chromosome 2q13 and

contains IL-1A, IL-1B, and IL-1RN (which encodes the IL-1 receptor antagonist) [14]. A case-control study has shown that there is no direct evidence confirming an association between IL-1β and IL-1RN gene polymorphisms and gastric cancer. However, people carrying the IL-1RN 2R allele may be at increased risk of developing gastric cancer [15]. IL-6 is mainly produced by mononuclear macrophages, endothelial cells, and lymphoid cells; it is a cytokine with multiple effects and plays an important role in the development and progression of gastric cancer. A previous study showed that IL-6-6331 in a Chinese population was associated the development and progression of gastric cancer [16]. However, the result of a meta-analysis showed that polymorphism at IL-6-174 C/G or IL-6-572 C/G was not associated with the risk of gastric cancer [17]. IL-10 is one of the inflammatory cytokines and plays an important role in the inhibition of inflammation and the prevention of tumors. Xue et al [18, 19] showed that the IL-10-592 AA and IL-10-819 TT genotypes in Asians were associated with a reduced development of gastric cancer and were protective factors. In patients infected with *H. pylori*, the IL-10-819 C allele and the IL-10-592 C allele could increase the risk of gastric cancer. In addition, IL-10 polymorphism and *H. pylori* infection had a synergistic effect [20].

TNFs are cytokines with a variety of biological activities in the body that play important roles in anti-tumor immunity. Hong et al [21] reported that the TNF-α-308 G>A polymorphism in a Chinese population is associated with the progression of gastric cancer. HLA antigens are cell surface proteins that interact with specific T-cell receptors. There are two groups of HLA genes, HLA1 (HLA-A) and HLA2 (HLA-DR, HLA-DQ, and HLA-DP). Ando et al [22] suggest that the HLA class II and IL-10-592A/C polymorphisms synergistically affect the susceptibility to gastric cancer development of H. pylori-infected individuals in the Japanese population. Huang et al. [23] also showed that the HLA-DQA1 gene was associated with susceptibility to gastric cancer; in addition, there was an additive and multiplicative interaction between *H. pylori* infection and environmental factors.

Gastric mucosal protective genes

The major genes that have gastric mucosal protective effects are mucin genes. Currently, the known subtypes include MUC1, MUC2, MUC5AC, MUC6, and the trefoil peptide family genes [24]. MUC1 is a transmembrane glycoprotein with a large molecular weight (2000 kDa). It forms a "mucus-bicarbonate barrier" together with HCO_3^- to protect the gastric mucosa [25]. Recently, Liu et al [26] performed a meta-analysis and demonstrated that the presence of the G allele at rs4072037 of the MUC1 gene may contribute to protection against gastric cancer in Asian.

The trefoil peptide family belongs to the trefoil factor family of peptides, which mainly consists of the breast cancer-associated pS2 peptide, trefoil factor family 1 (TFF1), spasmolytic polypeptide (SP), and intestinal trefoil factor (ITF) [27]. It is currently thought that trefoil peptides can interact or crosslink with mucins in mucus to form a mucinous gel to enhance the barrier defense capacity of the gastrointestinal mucosa, induce epithelial cell migration, promote the differentiation of normal and precancerous lesions, and promote the growth of tumor cells [28]. Recent studies showed that TFF2 gene polymorphisms were not associated with gastric cancer [29].

Metabolic enzyme genes

Metabolic enzyme genes that influence genetic susceptibility to gastric cancer mainly include the phase I metabolism-related cytochrome P450 enzyme (CYP450) system. This system can catalyze procarcinogens that enter the body into electrophilic compounds that can attack intracellular biological macromolecules to eventually form DNA adducts that activate carcinogenesis or mutagenesis. To date, genetic polymorphisms have been discovered in 7 CYP genes: CYP1A1, CYP2A6, CYP2C9, CYP2C18, CYP2C19, CYP2D6, and CYP2E1; of these, CYP1A1, CYP2E1, and CYP2C19 are the major genes associated with genetic susceptibility to gastric cancer [30]. Glutathione S-transferases (GSTs) are mainly associated with the phase II metabolic enzymes. These enzymes can catalyze the interaction between the intermediate metabolic products of exogenous compounds and reduced glutathione; in turn, reduced glutathione conjugates usually have reduced toxicity and are easily discharged from the body. Therefore, they play important roles in protecting cells from attack by chemical carcinogens [31].

A recent meta-analysis [32] indicated that CYP1A1 Ile/Val genetic polymorphisms, but not CYP1A1 Msp I polymorphisms, are associated with an increased digestive tract cancer risk in Chinese population. Another meta-analysis [33] suggested no associations between CYP1A1 Ile462Val polymorphism and gastric cancer, but possible associations between CYP1A1 MspI and CYP1A2*1 F polymorphisms and gastric cancer. Therefore, additional well-designed studies, with larger sample size, focusing on different ethnicities and cancer types are now warranted to validate the association between CYP1A1 polymorphisms and gastric cancer. As for GSTM1, Lao et al. [34] suggested that the null genotype of GSTM1 may be an important genetic risk factor for gastric cancer development, although it has been shown that GST polymorphism is not associated with individual susceptibility in a southern European population [35].

In addition to the above genes, it was recently discovered that polymorphism in specific genes that play important roles in the development and progression of gastric cancer, including cyclooxygenase 2 (COX-2) [36-39], 12-lipoxygenase (LOX12) [40-41], and superoxide dismutase (SOD) [42-45], might be associated with the development of gastric cancer.

DNA repair genes

DNA damage/repair has important significance in the development of gastric cancer. DNA repair enzymes play important roles in the maintenance of DNA stability. If DNA damage can accurately be determined and repaired, the body can metabolize normally. If repair enzyme genes have abnormalities, their repair functions will be affected, and the damaged DNA cannot be repaired or will contain errors, resulting in protein expression errors and inducing tumor development [46]. Major DNA damage/repair genes include methylenetetrahydrofolate reductase (MTHFR), X-ray repair cross-complementing 1 (XRCC1), and human homolog of the 8-oxoguanine glycosylase 1 (HOGG1).

MTHFR is a rate-limiting enzyme in the regulation of folate and methionine metabolism. Its polymorphism influences folate metabolism to cause a deficiency in methyl groups, thus promoting gastric cancer development. Using meta-analysis, a study showed that the C677T polymorphism of MTHFR with the TT genotype increased susceptibility, while the A1298C polymorphism with the CC genotype did not significantly increase susceptibility [47]. Studies on the XRCC1 polymorphism and gastric cancer are still in the initial stages, and there are still large discrepancies between studies. Currently, it has been shown that the XRCC1 gene has 3 polymorphic loci: C26304T (Arg194Trp) in exon 6; G27466A (Arg280His) in exon 9; and G28152A (Arg399Gln) in exon 10. Liu et al [48] performed a meta-analysis to show that the Arg399Gln polymorphism in XRCC1 was not a risk factor for developing gastric cancer. Pan et al [49] showed that carrying the XRCC1 Arg194Trp polymorphism was a genetic susceptibility factor of non-cardia gastric cancer in a Chinese Han population. The study of Kim et al [50] found that three alleles (Ser326, Cys326, and Gln46) of the HOGG1 gene could effectively inhibit chemical-induced oxidative mutagenesis of DNA to reduce the development of tumors. However, a meta-analysis in a different country showed that HOGG1 gene polymorphism was not associated with susceptibility to gastric cancer [51]. Duan et al [52] found that codon 312 in the human xeroderma pigmentosum group D (XPD) gene (also known as the excision repair cross-complementation gene, ERCC) was significantly associated with susceptibility to gastric cancer. Zhang et al [53] showed that the polymorphism rs744154 of the xeroderma pigmentosum gene (XPF) was associated with the development of gastric carcinoma and was associated with *H. pylori* infection in paracancerous gastric mucosa.

Tumor suppressor genes

The p53 gene has been confirmed to be an important tumor suppressor gene. In a previous study, Malakar et al [54] showed that the Arg/Arg allele of the p53 gene was associated with higher risk of gastric cancer, especially the diffuse type of gastric cancer. The results of a meta-analysis [55] showed that p53CD72 might be associated with a genetic susceptibility to gastric cancer; for Asians, it might also be an important biomarker. It has been shown that p53CD72 and *H. pylori* infection in the Gansu Province of China have a synergistic effect [56]. NM23 is the first confirmed tumor metastasis suppressor gene. Its encoded protein is a member of the nucleoside diphosphate kinase family. Its expression is closely associated with the

invasion and metastasis of tumors as well as with a poor prognosis [57]. It has been shown in recent years that NM23 gene expression is associated with the mechanism of gastric cancer progression [58].

Other gastric cancer susceptibility genes

In recent years, several new genes have been discovered to be associated with a genetic susceptibility to gastric cancer; for example, as a growth factor, transforming growth factor b (TGF-b) has been closely associated with the development and progression of a variety of tumors [59]. The results of a meta-analysis further indicated that TGF-b1-509T was a predisposing factor for gastric cancer [60]. Vascular endothelial growth-factor (VEGF) is a 32-34 kDa secreted glycoprotein with multiple functions. Its gene is located at the long arm of chromosome 6 (6p21.3). Studies have shown that VEGFA-634G/C contributes to the development of gastric cancer, while VEGFA+936C/T is not associated with gastric cancer [61, 62]. Adiponectin is a hormone protein that has several biological functions such as the regulation of energy balance, the enhancement of insulin sensitivity, anti-inflammation, and anti-atherosclerosis. Compared with the normal population, gastric cancer patients have lower levels of serum adiponectin [63]. Ye et al. [64] showed that polymorphism in the ADIPOQ gene might be associated with the development of gastric cancer. Recently, Shirai et al [65] discovered that p73 genetic polymorphism might increase the risk of gastric cancer, especially the diffuse cancer type; however, the function of the p73 gene still requires further study.

Conclusion

Genetic susceptibility genes for gastric cancer play very important roles in the development and progression of gastric cancer. Although the pathogenesis and genetic mechanisms of several genes have been elucidated recently, further large-sample studies are required after the meta-analysis of many genes. In addition, different populations in different regions with different races will have certain differences in genetic susceptibility. Therefore, further in-depth studies are needed to search for gene therapy methods to eventually provide a scientific basis for the prevention and control of gastric cancer.

Disclosure of conflict of interest

None.

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