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REVIEW

Genetic Basis of Gastric Cancer

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Abstract Gastric cancer is the result of multiple risk factors, including environmental factors, genetic factors and the interaction between them. The environmental factors mainly include dietary, Helicobacter pylori infection and family history of gastric cancer. Genetic factors mainly refer to the susceptible genes that cause epigenetic alterations in oncogenes, tumor suppress genes, cell cycle regulators, DNA repair genes and signaling molecules. This paper summarizes the susceptible genes of gastric cancer and explores the genetic basis of it.

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Gastric cancer is the result of complex interaction of environment and multiple genes. The evident risk factors of gastric cancer include dietary, the Helicobacter pylori infection, the family history and the genetic factors.[1, 2] Though there is great progression in the diagnose and treatment of gastric cancer, the survival rate is still stagnant and poor, only about 20 percent of patients with gastric cancer can reach five-year survival. So a systematic view of the genetic basis of gastric cancer is necessary to help establish new strategies for prevention and treatment of gastric cancer. Genetic factors mainly refer to the susceptible genes of cancer that are involved in multiple genetic and epigenetic alterations of oncogenes, tumor suppressor genes, cell cycle regulators, DNA repair genes and signaling molecules.[3]

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ONCOGENES

Oncogenes are genes whose normal activity promotes cell proliferation. Oncogenes function through the mechanism of gene mutation, gene insertion, chromosomal translocation, gene amplification and DNA hypomethylation. Oncogenes can be classified into five broad classes: secreted growth factors; cell surface receptors; components of intracellular signal transduction systems; DNA-binding nuclear proteins; components of the network of cyclins, cyclin-depen-dent kinases (CDKs) and kinases inhibitors that govern progress through the cell cycle.[4]

C-Met

C-Met, known as hepatocyte growth factor receptor, is encoded by a proto-oncogene, which is a membrane tyrosine kinase. C-Met gene locates at 7q31, and its product of transcription is a 6-kb mRNA, playing an important role in the intracellular signal transduction. Presently, researchers

believe that C-Met can participate in the process of tumor invasion and metastasis. C-Met expression is positive in 82 percent of poorly differentiated gastric cancer and 50 percent of highly differentiated one. Its expression is evidently associated with the lymphatic metastasis of gastric cancer.[5] The amplifying of C-Met is related to the progression of gastric cancer. A study which detecting the expression of C-Met protein in 78 cases of gastric cancer tissue by immunohistochemical methods found that the C-Met expression was significantly related to the size, differentiation degree, infiltration depth, and lymph node metastasis. The C-Met was positively expressed in 77.9% of primary lesion of gastric cancer which has lymph node metastasis. The expression of C-Met in gastric cancer could promote the proliferation and metastasis of tumor cells.[6] Study of gastric mucosa precancerous lesions and C-Met gene expression in gastric cancer tissue revealed that C-Met gene has low expression in superficial gastritis, its expression gradually increased while the lesion developing from gut to hyperplasia, and then evolution of cancer; the advanced gastric cancer has the most significant expression.[7] So the oncogenesis of gastric cancer is associated with the expression of C-Met proto-oncogene. C-Met may have a synergic effect with osteopontin (OPN) and matrix metalloprotein-9 (MMP-9) in gastric cancer.[8]

C-erb-B_2

C-erb-B_2 gene is located at 7q21 and its product of transcription is a trans-membrane glycoprotein which could function as a tyrosine kinase. C-erb-B_2 gene seldom mutates, and is overexpressed in human gastric cancer. Motojima *et al*[9] used a multiple factors analysis model to assess the recurrence of gastric cancer and discovered that C-erb-B_2 positive expression was an independent predictor of recurrent disease. Youemura *et al*[10] found that in C-erb-B_2 positive patients, the relative risk of death and recurrence was 3 to 5 times higher than that in C-erb-B_2 negative patients, and COX model analysis showed that C-erb-B_2 was an independent factor that affect the outcome of gastric cancer. Most researchers believe that the expression of C-erb-B_2 gene plays an important role in the malignant transformation of gastric cancer, lymph node metastasis, tumor proliferation infiltration, as well as some benign pathological changes of stomach.[11] It is suggested that the overexpression of C-erb-B_2 gene in gastric cancer has correlation with clinical pathologic staging, histological grade and lymph node metastasis.[12]

Bcl-2

Bcl-2 gene is the first gene that was found as apoptosis inhibiting gene. The encoded protein is located on the mitochondrial membrane, endoplasmic reticulum retinal and nuclear membrane. The main function of Bcl-2 is to prolong the life of the cell and increase the cell resistance to apoptosis stimulating factors.[13] It makes cells survive after DNA damage, gather mutation products together, and promote the generation and development of tumor. Studies have found that transgenic mice with overexpression of Bcl-2 was more prone to cancer.[14]

Chou *et al*[15] have found that SC-M gastric cancer cell lines transfected with Bcl-2 can accelerate retinoic acid induced growth suppression of SC-M cells, and Bcl-2 can make the transfected SC-M cells to stop growing 2 days earlier than those cells without transfection. These results indicated that the over expression of Bcl-2 may not only inhibit the apoptosis, but also can inhibit the growth of cells at the same time. Kim *et al*[16] found that decreasing the expression of Bcl-2 by RNA interference in MCG-803 gastric cancer cells induced cells apoptosis. Flow cytometry demonstrated the ratio of G0 stage arrest was 17 times higher than the untreated cells, suggesting that inhibiting Bcl-2 expression has a potential application value in treatment of gastric cancer.

TUMOR SUPPRESSOR GENES

P53

P53 gene encodes a 53 kD protein and functions as a regulator of DNA transcription. It bounds directly to DNA and recognizes DNA damage. P53 can induce cell cycle arrest in G1 stage, allow time for DNA to repair when DNA damage is "considered" repairable. When DNA is too excessively damaged to repair, P53 can promote apoptosis to prevent the cell which has an impaired DNA sequence from proliferating as a defective or malignant clone.[13] Fifty percent of human cancers are associated with p53 gene mutation. Zhu *et al*[17] found that no expression of P53 was detected in normal gastric mucosa epithelium, while the abnormal expression of P53 was found in the early stages of gastric mucosal cancer. When the gastric cancer lesions are aggravating, the expressional level of P53 rise throughout the whole cancer process.[18] Sirak *et al*[19] examined P53 expression in 357 patients cases of gastric cancer by immunohistochemical techniques, and found that prognosis of the patients who had positive expression of P53 were significantly worse than those with negative expression of P53, indicating that the over expression of mutant p53 attenuates the inhibition of cancer cells proliferation and promotes invasion and metastasis. It was reported that over expression of p53 and mutation of p53 in gastric