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Genetic and Epigenetic Changes of CDKN2A in Gastric Cancer

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Review

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ABSTRACT

Gastric cancer is a multifactorial heterogeneous disease involving various subgroups with different molecular features and it is one of the leading causes of cancer deaths worldwide. Although dietary conditions (fried, fatty and salty foods), tobacco and alcohol consumption, and some gastrointestinal infections are important in gastric cancer, the development of the disease is complex. It is clear that tumor suppressor genes and proto-oncogenes have a significant impact on the formation of gastric cancer. CDKN2A is a tumor suppressor gene that encodes two different proteins, and methylation, deletion and other mutations of this gene are effective in both the development and prognosis of gastric cancer. CDKN2A hypermethylation is common in gastric cancer related with H. Pylori and EBV infections. A connection is often established between metastases of gastric cancer and losses of this tumor suppressor gene (deletions). In this context, possible changes in the CDKN2A gene should be taken into consideration as a biomarker in the treatment and follow-up of gastric cancer.

Keywords: Gastric cancer, tumor suppressor gene, CDKN2A, methylation, deletion

Gastrik Kanserde CDKN2A'nın Genetik ve Epigenetik Değişiklikleri

Derleme

Süreç

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ÖZET

Mide kanseri, farklı moleküler özelliklere sahip çeşitli alt grupları içeren multifaktöriyel, heterojen bir hastalıktır ve dünya çapında kanser ölümlerinin önde gelen nedenlerinden biridir. Gastrik kanserde beslenme koşulları (kızarmış, yağlı ve tuzlu yiyecekler), tütün ve alkol tüketimi ve bazı gastrointestinal enfeksiyonlar önemli olmasına rağmen hastalığın gelişimi karmaşıktır. Tümör baskılayıcı genlerin ve proto-onkogenlerin mide kanserinin oluşumunda önemli bir etkiye sahip olduğu açıktır. CDKN2A, iki farklı proteini kodlayan tümör supresör bir gendir ve bu genin metilasyonu, delesyonu ve diğer mutasyonları mide kanserinin hem gelişiminde hem de prognozunda etkilidir. CDKN2A hipermetilasyonu, H. Pylori ve EBV enfeksiyonlarıyla ilişkili mide kanserinde yaygındır. Mide kanserinin metastazları ile bu tümör baskılayıcı genin kayıpları (delesyonlar) arasında sıklıkla bir bağlantı kurulmaktadır. Bu bağlamda, mide kanserinin tedavi ve takibinde biyobelirteç olarak CDKN2A genindeki olası değişiklikler göz önüne alınmalıdır.

Anahtar Kelimeler: Mide kanseri, tümör supresör gen, CDKN2A, metilasyon, delesyon

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Introduction

Gastric cancer (GC), a heterogeneous disease with sophisticated pathogenesis and regional variability, is one of the most common causes of cancer-related deaths worldwide.[1] GC patients are often diagnosed late and most of them are in an advanced stage at the time of diagnosis.[2] Some conditions such as high salt intake, smoking and alcohol consumption, Helicobacter pylori (H. pylori) infection are among the risk factors.[3] Pathologically, adenocarcinomas constitute more than 95% of the malignancies in the stomach, and the remaining rare neoplasms are lymphomas, sarcomas etc.[4] Gastric cancers can be classified as sporadic GC (majority of GC, usually over 45 years of age), early-onset GC (about 10%, predominance of genetic factors), gastric stump cancer (after gastrectomy), and hereditary diffuse GC (1–3% of all GCs).[5] These cancers are actually classified histologically as intestinal and diffuse (Lauren classification) or papillary, tubular, mucinous, and poorly cohesive (WHO classification).[6] Depending on the location of the tumor, it can also be grouped as cardial and distal.[7]

Etiology of Gastric Cancer

Environmental factors such as H. pylori infection, dietary conditions and lifestyle are often involved in the intestinal type of gastric cancer, however genetic abnormalities are more blamed in the diffuse type.[8] Intestinal type gastric cancer may occur with H. pylori infection accompanied by intestinal metaplasia and atrophy, but the diffuse type is usually caused by pangastritis, in which atrophy is not observed.[9] Smoking and excessive alcohol consumption have a significant importance in the development of gastric cancer. The presence of bacteria or viruses is clear in the etiology of gastric adenocarcinomas. While a significant portion of GC cases are associated with H. pylori, about 10% may result from Epstein Barr Virus infection.[10] Although most gastric cancers occur sporadically, approximately 5-10% of cases may be familial, such as hereditary diffuse gastric cancer, familial intestinal gastric cancer, etc.[11] Autoimmunity is also somehow related to gastric carcinogenesis, and diseases with an autoimmune basis, such as systemic lupus erythematosus, pernicious anemia, and type 1 diabetes, may be associated with the risk of GC.[12]

Genetics of Gastric Cancer

Cancer is a genetic disorder that involves alterations in tumor suppressor genes and protooncogenes and these genes significantly contribute to the development of malignancy through loss or gain of function.[13] Genetic changes that lead to cancer may arise from errors in DNA replication and cell division, epigenetic disorders, poor dietary conditions and DNA damage caused by harmful elements including cigarette and ultraviolet, or the problem may emerge through germline mutations from parents. Although gastric cancer is a common malignancy in the world, its molecular characteristics are not yet fully understood.[14] In fact, genetic, epigenetic and environmental elements act collectively and are effective in the formation and progression of the disease in gastric cancer.[15] GC, which is closely related to some genetic alterations, usually develops on the basis of activation in proto-oncogenes and/or inactivation in tumor suppressor genes.[16] Genes such as KRAS, PIK3CA, EGFR, ERBB3-4 with oncogenic activity and p53, CDKN2A, CDH1 with tumor suppressor activity are often mutated in various cancers, including gastric cancer.[17] Mahmud et al. emphasized that some HLA gene polymorphisms may be positively or negatively associated with the progression and mortality of H. pylori-related GC in certain populations.[18]

Tumor Suppressor Genes and CDKN2A Gene

Tumor suppressor genes (TSGs) regulate cell division by inhibiting cell proliferation. These genes also may promote apoptosis or may contribute to DNA repair. Some of the relevant genes can perform all of these functions. Therefore, TSGs have a significant effect in preventing cancer development. Tumor suppressor genes are in balance with proto-oncogenes in the organism in terms of the cell cycle and various signaling pathways. Proto-oncogenes have a dominant nature and mutation of a single allele may be sufficient for the development of cancer. However, TSGs have a recessive nature and both alleles must mutate for loss of function (two hit hypothesis). Loss-of-function mutations in TSGs may lead to cancer formation or progression of existing cancer.[19] Various tumor suppressor genes with different functions are found in humans, such as Rb1, p53, CDKN2A, PTEN, VHL, APC, NF1, NF2, BRCA1 and BRCA2. These genes undergo mutation, methylation or deletion in many cancers.

There are two major TSGs called CDKN2A and CDKN2B located on the short arm of chromosome 9 (9p21.3). CDKN2A is one of the most frequently inactivated TSGs, and its inactivation plays an important role in various common malignancies.[20] On this basis, it is also possible to encounter CDKN2A gene mutations, deletions and methylations in gastric cancer. Methylation is an epigenetic condition that leads to gene silencing. In a study by Xu et al., it has been noted that the hypermethylation of CDKN2A gene was significantly higher in GC than in non-tumor tissues.[21] On the other hand, somatic mutations of CDKN2A have been found to occur frequently in HPV-negative vulvar squamous cell carcinomas.[22] The CDKN2A gene encodes two distinct tumor suppressor proteins called $p16^{INK4a}$ and $p14^{ARF}$. Although these two proteins carry a different first exon in their structure (exon 1α & exon 1β), exons 2 and 3 are identical.[23] p16 blocks cell cycle progression by inhibiting two cyclin-dependent kinases (CDK4, CDK6) during the G1 to S transition in the cell cycle.[24] While MDM2 inhibits p53 by inducing its degradation via the proteasome, $p14^{ARF}$ prevents MDM2-mediated disruption of p53 by sequestering MDM2 and thus blocking MDM2-p53 interaction.[25] In the context of p53 protection, it is necessary to acknowledge that $p14^{ARF}$ is a tumor suppressor protein. Indeed, promoter methylation of $p14^{ARF}$ has been identified in a wide variety of human cancers, including gastric, colorectal, and prostate carcinomas.[26] The gene named CDKN2B encodes $p15^{INK4b}$ and Tu et al. state that inactivation of this tumor suppressor has a critical importance in pancreatic tumorigenesis.[27] Since CDKN2A and CDKN2B are located adjacently on the same region, co-deletions of CDKN2A and B may occur in various cancers.[28]

Epstein–Barr virus-associated gastric cancer (EBVaGC), a common malignancy related to EBV infection, display promoter hypermethylation of the CDKN2A gene.[29] Once viral DNA reaches a cell, it can be deactivated by methylation that also disrupts surrounding host DNA. This effect can be emerge even at the genomic level and lead to inactivation of tumor suppressor genes.[30] CDKN2A gene promoter methylation and p16 protein loss are much higher in gastric cancers with EBV than in tumors without EBV.[31] As a result, it has been shown that there is a close relationship between EBV and hypermethylation of the CDKN2A gene, and it has been reported that some of the gastric cancers contain EBV in the cancer cells.[32] In a study by Alves et al., inactivation of CDKN2A by promoter methylation in the DNA obtained from H. pylori positive gastric cancer samples was an important finding, especially in the diffuse subtype.[15] Intestinal metaplasia is accepted as a premalignant lesion of the gastric mucosa and most of the methylation sites in this condition, including CDKN2A, have also been shown to be hypermethylated in intestinal type GC.[33]

Deletions of CDKN2A

The loss of tumor suppressor genes plays an important role in the etiopathogenesis of cancers. In this context, CDKN2A gene deletions are frequently encountered in various malignancies. Homozygous deletion of CDKN2A can be seen in a significant proportion of diffuse pleural mesotheliomas via fluorescence in situ hybridization[34] and patients with this deletion have a worse survival compared to cases without this abnormality.[35] Similarly, a high frequency of homozygous deletions in the CDKN2A gene has been reported for anaplastic meningiomas.[36] Some studies suggest that homozygous deletion of CDKN2A in glioblastoma indicates a worse prognosis and these cases may profit from high doses of radiation.[37] In a study of Boşoteanu et al., homozygous deletion or monosomy of CDKN2A was detected in most cases of multiple primary melanoma and/or familial cutaneous melanoma.[38] Since CDKN2A is disabled in a remarkable proportion of melanomas (40-70%), treatments targeting CDKN2A loss provide a significant advantage for the intervention in melanoma.[39] CDKN2A deletions occur in human cancers, including gastric cancer, with inactivation of $P16^{INK4A}$ and $P14^{ARF}$, and these deletions are frequently encountered in the metastasis of GC.[40] Homozygous deletions of CDKN2A also increase angiogenesis.[41] Somatic copy number deletion (SCND) of CDKN2A has been reported to be highly associated with hematogenous metastasis of GCs and it has also been described that CDKN2A deletion can inhibit the expression of P53 and promote the phosphorylation of RB1.[42]

Although CDKN2A is a tumor suppressor gene, there are also studies that express its position differently in various cancers. For example, in a study by Zhu et al., the expression of CDKN2A was upregulated in hepatocellular carcinoma (HCC) tissues compared to non-tumor tissues, and HCC patients with high CDKN2A expression were shown to have poor survival.[43] Additionally, in a study by Hosny et al., it was determined that p16 tumor suppressor was overexpressed in almost all malignant ovarian germ cell tumors.[44] On the other hand, since p16 and Rb (Retinoblastoma) genes are two major components of the Rb pathway, it has been suggested that physiological deactivation of pRB in G1 phase will result in increase of p16 expression, thus pRb-negative tumors may exhibit high p16 expression.[45] However, the mechanism and genetic background of the upregulation or overexpression mentioned in these studies, and even the association of high CDKN2A expression with poor survival are not clear. Indeed, Wang et al declare that $p16^{INK4a}$ mRNA expression is significantly downregulated in GC tissues compared with normal tissues[46] and Oue et al suggest that silencing of CDKN2A by CpG hypermethylation is frequently seen in intestinal type GC.[33] Furthermore, cancers that develop on a viral basis contain a methylation pattern associated with downregulation of CDKN2A (p16), and EBV-positive gastric tumors may develop with hypermethylation of the CDKN2A promoter.[47] Additionally, loss of CDKN2A has been declared as one of the most common somatic copy number alterations in Chinese GC samples.[48] Although there is a decrease in overall survival in patients with CDKN2A methylation, and therefore low CDKN2A expression, larger studies and bioinformatic analyzes are needed to determine the clinical and molecular significance of CDKN2A hypermethylation clearly in GC.[21]

In conclusion, it is possible to state that CDKN2A mutations, deletions and methylation have a great importance in gastric cancer cases, both in terms of diagnosis and treatment and the course of the disease. CDKN2A deletions are associated with poor prognosis in gastric cancer and may even be responsible for gastric cancer metastases. It can be declared that the methylation profile of the CDKN2A gene is also effective as well as CDKN2A losses in gastric cancers. In this context, gastroenterologists, oncologists and medical geneticists should be in cooperation in the diagnosis and follow-up of gastric cancer cases.

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