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Progress in the Study of Esophageal Cancer-Related Genes and Their Therapeutic Modalities

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Abstract

Esophageal cancer is a prevalent malignant tumor of the digestive tract that has a high mortality rate, posing a severe threat to human life. The development of esophageal cancer is the result of multiple factors, and the process of carcinogenesis is accompanied by abnormal expression of several genes. Mutations in oncogenes and tumor suppressor genes result in changes in their expression and activity, playing a crucial role in the occurrence, development, pathological staging, and prognosis of esophageal cancer. This paper aims to review and study recent research on esophageal cancer, including basic information, related genes, and treatment modalities, in order to explore new ideas and research bases for the diagnosis and treatment of esophageal cancer.

Keywords: esophageal cancer; pathogenesis; gene study; treatment modality; research progress

1. Introduction

Esophageal carcinoma is one of the most common malignant tumors of the gastrointestinal tract globally. According to the WHO histological classification, esophageal cancer includes squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC), of which SCC accounts for approximately 90% of cases. China has a high incidence of esophageal cancer, with an annual average of approximately 150,000 deaths, accounting for 21.8% of the national tumor mortality rate (He QW, Sun FG, Zeng Y, et al., 2022). Esophageal cancer is the fourth leading cause of cancer-related deaths, and China has one of the highest mortality rates for this disease. The age of onset of esophageal cancer is typically above 40 years old, and it affects more men than women. The exact cause of esophageal cancer is not well understood, but it is found to be closely associated with several factors, including stimulation by carcinogenic chemicals, inflammation and trauma, genetics, and lifestyle (Long D D, Peng W L, Zhou R, et al., 2022). Currently, the treatment of esophageal cancer primarily relies on surgery, radiotherapy, and chemotherapy, all of which have unsatisfactory effects and high mortality rates. This paper aims to review the pathogenesis of esophageal cancer, related genes, and treatment modalities to provide a reference for further in-depth research on the treatment of esophageal cancer.

2. Basic Overview of Esophageal Cancer

The early symptoms of esophageal cancer are often not obvious or severe, making them difficult to detect. Generally, patients may experience a burning or pinching pain behind the sternum when swallowing food, especially when consuming rough, hot, or irritating food. They may also experience a sensation of choking or a feeling of a foreign body in their throat, often related to the patient's emotions and the type of food consumed. Patients may notice slow food passage, with a sense of stagnation or even the appearance of food sluggishly stuttering downward. However, these symptoms often disappear on their own, only to reappear at intervals. As the disease progresses, patients may experience progressive difficulty in swallowing, and choking may occur when eating food, which requires the use of soup and water to aid in swallowing. Eventually, patients may only be able to consume liquid food, and it may become difficult to drink water. Furthermore, due to the obstruction of saliva and esophageal secretion, the tumor cannot enter into the stomach, causing patients to vomit a lot of mucus and food after meals (Radovic S, Doric M, Hukic A, et al., 2013). Patients may also experience persistent back pain and malnutrition due to long-term difficulty in eating. In the later stages of the disease, esophageal cancer patients are in extremely poor physical condition, often experiencing multi-organ damage. As the tumor spreads and invades adjacent organs, patients may experience symptoms such as esophageal tracheal fistula, mediastinal abscess, pneumonia, and lung abscess. When metastatic lymph nodes compress the trachea, laryngeal nerve, and phrenic nerve, patients may experience difficulty breathing, hoarseness, and contradictory movement of the diaphragm. Patients with advanced esophageal cancer may also suffer from a series of complications such as vomiting blood, blood in stool, and even esophageal perforation.

3. Pathogenesis of Esophageal Cancer

Most esophageal cancers are caused by the proliferation of the esophageal epithelium, leading to atypical proliferation. Although the pathogenesis of esophageal cancer remains unclear, continuous research on the cell growth cycle has revealed that human cells contain various oncogenes and tumor suppressor genes, which regulate the cell cycle. If these genes become dysfunctional or out of control, they can lead to the development of esophageal cancer and other tumors. Three key factors have been identified: first, abnormal functions of oncogenes can cause dysfunction of cellular signaling pathways; second, changes in tumor suppressor genes play an important role in DNA repair, cell proliferation, and apoptosis; and third, abnormal G1/S detection sites (transitions from G1 to S phase in the cell cycle) can cause a loss of control of the cell cycle (He QW, Sun FG, Zeng Y, et al., 2022). Therefore, the correlation between oncogenes and tumor suppressor genes and esophageal cancer is significant for the diagnosis, treatment, and prevention of clinical esophageal cancer.

4. Expression of Esophageal Cancer-Related Genes

Oncogenes are products encoded in cells or viruses that promote the malignant transformation of normal cells. Under normal physiological conditions, the activity and content of oncogene expression products are strictly regulated by the internal and external environment, and they do not cause abnormal cell proliferation. However, mutations can result in excessive activity or content, leading to the development of tumors. Tumor suppressor genes are a class of genes that play a negative regulatory role in cell growth, inhibiting malignant cell growth. Abnormal expression of oncogenes and tumor suppressor genes has been shown to be closely related to the development of esophageal cancer (Long D D, Peng W L, Zhou R, et al., 2022).

4.1 Traditional Medical Treatment Theory

4.1.1 RAS Gene

RAS genes are a class of proto-oncogenes discovered in rat sarcoma virus, which encode a 21 KD immune-related protein called p21s protein or RAS protein. RAS proteins are GDP/GTP binding proteins and are intracellular signal transducers. In wild-type cells, RAS plays a critical role in regulating proliferation, differentiation, and senescence. The RAS gene family includes three genes: KRAS, NRAS, and HRAS, with the KRAS gene being the most easily activated oncogene (Guo F, Gong H, Zhao H, et al., 2018). Some scholars (Wei L & Yang Zhaoxia, 2022) have used the experimental method of immunohistochemistry to detect the expression of RAS protein in 50 esophageal cancer tissue specimens, among which the

positive expression rate was 32%. Based on the experimental results, it can be inferred that the expression level of RAS protein can be used to assess the prognosis of patients with esophageal squamous cell carcinoma.

4.1.2 NM23 Gene

The NM23 gene is a previously identified tumor metastasis suppressor, and its expression level is closely related to tumor invasion, metastasis, and the progression of the patient's disease. The NM23 gene is located on human chromosome 17 (17q21.3), and its product is a 17KD nucleoside diphosphate kinase (NDPK) (Radovic S, Doric M, Hukic A, et al., 2013). According to the literature (Wen E, Qin T & Peng J., 2020), the expression of NM23 gene in esophageal squamous carcinoma specimens and normal mucosal tissues adjacent to the carcinoma was detected using SP immunohistochemistry assay, and it was confirmed that the expression of NM23 gene was significantly lower in esophageal carcinoma tissues than in normal tissues. Abnormal expression of the NM23 gene was found to be strongly associated with the development of esophageal carcinoma. Furthermore, it has been reported that the NM23 gene may play a positive regulatory role in inhibiting the formation, invasion, and metastasis of esophageal cancer, as well as promoting the differentiation of esophageal cancer (Jiang H, Li B, Wei YF, et al., 2014).

4.1.3 COX-2 Gene

The cyclooxygenase-2 (COX-2) gene is an inducible cyclooxygenase that is not normally expressed in most tissues. However, COX-2 can show high expression in tissues induced by inflammation, tumors, and other conditions. Highly expressed COX-2 can catalyze the production of prostaglandin (PG) E2 from arachidonic acid. PGE2 can inhibit the apoptosis of tumor cells, increasing the proliferative activity of tumor cells and weakening the immune surveillance of natural killer cells in vivo, ultimately leading to the induction of cancer (Song Yipeng & Li Minghuan, 2012). Kumagai Y et al. (Kumagai Y, Sobajima J, Higashi M, et al., 2015) showed that microvessel density in esophageal squamous carcinoma was positively correlated with the expression of the COX-2 gene.

4.1.4 C-Met Gene

The transmembrane receptor c-Met protein has a role in phosphorylation activity. The c-Met gene is associated with various oncogene products and regulatory proteins, and it plays an important regulatory role in the proliferation and differentiation of cancer cells. Chuntao Liu et al. (Liu CHT, Zhu ST, Tian Y, et al., 2012) collected pathologically confirmed esophageal cancer and paraneoplastic tissue specimens and examined the expression of c-Met using immunohistochemical assays. The results showed that the expression of the c-Met gene was elevated in esophageal squamous carcinoma tissues and was significantly associated with lymph node metastasis and TNM stage of patients. Similarly, Yan Chen et al. (Chen Y, Song S, Tang S, et al., 2018) selected 80 esophageal cancer specimens and used paraneoplastic tissue specimens as the control group. The two groups were examined by immunohistochemistry, and the positive expression of the c-Met protein in esophageal cancer tissues was elevated and closely related to the clinical stage, lymph node metastasis, and depth of infiltration of patients.

4.1.5 P27 Gene

The P27 gene is an important gene discovered by Polyak et al. in 1994. This gene, which regulates the cell cycle and inhibits cell division, is found in region 1, band 3 (12p13) of chromosome 12 and encodes a protein containing 198 amino acids. It consists of two exons and two introns. P27 plays an important negative regulatory role in the cell cycle, preventing cells from passing through the G1/S phase, thus blocking the cell cycle process, and inhibiting cell proliferation. Ji Wei et al. (Ji W & Wang XY, 2018) used immunohistochemistry to detect P27 expression in 100 esophageal cancer specimens and found reduced expression of this gene in esophageal cancer tissues. Chen Jiesheng et al. (Chen J S & Wu M Y, 2015) used an immunohistochemical approach to study the expression of P27 protein in mucosa with normal cut edges, epithelium of the paracancerous mucosa, and carcinoma in situ on resected specimens of esophageal cancer. They found that the expression of the P27 protein gradually decreased in normal, proliferating, and malignant esophageal mucosal epithelial cells.

4.1.6 MTA1 Gene

The MTA1 gene is a tumor-infiltrating metastasis candidate gene located on human chromosome 14q23.3, with a full length of 2.2

KB. The family contains six different isoforms: MTA1, MTA1s, MTA1-ZG29p, MTA2, MTA3, and MTA3L. The MTA1 gene can regulate the transcriptional expression of target genes in a transcription factor-dependent manner, which in turn promotes gene transcription and improves protein stability (Salot S, Gude R., 2013). Chenxu Liu et al. (Liu C X, Zhou B., 2013) studied esophageal cancer and paraneoplastic tissues using immunohistochemistry and showed that elevated expression of MTA1 promoted the growth of esophageal cancer and enhanced the metastatic ability of lymph nodes. Similarly, Zhang Qiu et al. (Zhang Qiu & Wan Tao, 2017) selected 84 esophageal cancer specimens and 20 normal esophageal tissues, and used immunohistochemical staining for control analysis. They confirmed that the elevated expression of MTA1 gene in esophageal cancer tissues was closely related to the prognosis of patients.

4.1.7 CDK4 Gene

The CDK4 gene, also known as cell cycle dependent kinase 4, is a cell cycle regulator that is associated with tumorigenesis and progression when activated or expressed at high levels (Liu M, Liu H, & Chen J., 2018). The expression of CDK4 in esophageal cancer and paraneoplastic tissues was examined using immunohistochemical staining (Ji H-Z., 2018). The positive rates of CDK4 in esophageal and paraneoplastic tissues were 72% and 34%, respectively, showing significant differences between the two groups ($P<0.01$). These findings suggest that CDK4 can be used as a tumor marker for patients with esophageal cancer.

5. Treatment

5.1 Surgical Treatment

Surgery is the preferred method for treating esophageal cancer, particularly in the early stages. Once a patient is diagnosed, surgery should be performed as soon as possible. There are two types of surgery based on the condition: palliative surgery and radical surgery. Palliative surgery is mainly for patients in advanced stages or after radiotherapy who cannot be treated radically, including esophagogastric diversion, gastrostomy, and esophageal lumen built-in esophagus. On the other hand, radical surgery involves removing most of the esophagus, with the resection being at least 5 cm from the tumor.

5.2 Radiotherapy

Radiation therapy is a primary and effective treatment for esophageal cancer that is considered safe. This treatment involves the use of ionizing radiation to kill tumor cells while minimizing harm to normal tissues and cells by administering precise doses of radiation (Luo H-T, & Wang S-H., 2018). Radiation therapy is classified into extracorporeal and intracavitary irradiation. External radiation is the primary form of radiation therapy for esophageal cancer, whereby high-energy X-rays are administered to the esophageal lesion through the body surface once a day, five times a week, at 180-200 cGY/time. Intraluminal radiation, on the other hand, involves delivering radiation through a catheter to the esophageal luminal lesion via the nasal cavity. This type of radiation is beneficial for protecting normal tissues and enhancing the local tumor control rate. Currently, comprehensive radiotherapy is generally used to improve the treatment effect, such as preoperative radiotherapy, postoperative controlled radiotherapy, and simple pain-relieving radiotherapy.

5.3 Chemotherapy

Commonly used chemotherapeutic agents include Adriamycin (ADM), 5-Fluorouracil (5-Fu), Methotrexate (MTX), Cisplatin (DDP), Kepto (CPT-11), etc. The commonly used regimen of combination chemotherapy is DDP with 5-Fu. The combination of DDP increases the sensitivity of depleted oxygen cells and inhibits the repair of sublethal damage and potentially lethal damage, and 5-Fu kills tumor cells altering tumor cell proliferation kinetics and enhancing radiosensitivity (Liu YM, Jiao DC, Xu KH, et al., 2022). In recent years, the purple-shirt combination chemotherapy method has achieved encouraging results in the treatment of esophageal cancer.

5.4 Combined Multidisciplinary Treatment

In clinical settings, the combination of surgery and radiotherapy, as well as staged simultaneous radiotherapy and comprehensive treatment, are significantly more effective than palliative treatment alone. Furthermore, the use of intraesophageal stent placement is valued as a new treatment option by patients and physicians. Stenting can relieve esophageal obstruction, while heating of the stent through local thermotherapy can inhibit the continued growth of the tumor and activate the body's immune response. Additionally, stenting can be

combined with radiotherapy and chemotherapy for comprehensive treatment, making it a promising new treatment approach (Liu Jiayi, 2011).

5.5 Chinese Medicine Treatment

In recent years, Chinese medicine has made significant progress in the treatment of esophageal cancer. Chinese medicine practitioners typically attribute the disease to deficiency, depression, phlegm, and stasis, and apply discriminative treatment and recuperation accordingly. Several studies have classified esophageal cancer into four types based on Traditional Chinese Medicine (TCM) discriminative treatment methods: liver and qi stagnation, heat and toxicity injuring yin, qi stagnation and blood stasis, and qi and blood deficiency (Lou YN, & Jia LQ., 2013; Wang C Q, Wang G J., 2014; Pan F., 2022). Jin Long capsule, a Chinese herbal medicine, has been used to treat 60 cases of esophageal cancer, with a total efficiency rate of 75%, a lesion reduction rate of 33%, and an average survival period of 25.4 months. Furthermore, Chinese medicine has been used as an adjuvant treatment, combined with radiotherapy or surgery, to improve and stabilize the body's immune function and enhance tolerance to surgery, radiotherapy, or chemotherapy.

5.6 Others

In population intervention studies, combined dietary supplementation with B-carotene, A-tocopherol, and selenium was found to significantly reduce esophageal cancer incidence and mortality (Chen HH, & Wang HY., 2021). Although the mechanisms of vitamins and trace elements for the chemoprevention of esophageal cancer are not fully understood, a balanced diet has a definite effect on the prevention and adjuvant treatment of esophageal cancer. In an increasingly humanized medical environment, psychological care is gradually being emphasized. Esophageal cancer patients often experience anxiety about the difficulty in eating and losing weight, and their desire for survival makes them eager to recover. However, they may also experience negative emotions such as tension, fear, and insomnia about the safety of anesthesia and surgery, surgical effects and complications, and postoperative pain. Therefore, implementing psychological guidance, emotional comfort, and spiritual support to help patients remain emotionally stable, face their condition optimistically, establish confidence to overcome the disease, and actively cooperate with treatment is crucial.

6. Prevention

Preventing esophageal cancer is the most fundamental approach to controlling the disease, which involves three stages according to the multi-stage nature of cancer development: initiation, promotion, and evolution. First, adopting healthy eating habits is crucial. Chewing and swallowing slowly and consuming a balanced diet that provides sufficient nutrients, including protein, vitamins, and trace elements, are recommended (Chen HH, & Wang HY., 2021; Cao Yang, 2020). Second, regular checkups are important to detect and diagnose potential precancerous lesions early. Finally, maintaining an optimistic attitude towards life, engaging in physical exercise, and improving overall fitness can not only help prevent esophageal cancer but also benefit overall health.

7. Conclusion

Overall, while progress has been made in the treatment of esophageal cancer through surgical, radiation, and Chinese medicine techniques, there is still much to be understood about the disease and its biological changes. The development of new treatment ideas and approaches should be combined with a comprehensive analysis and research of the pathogenesis of esophageal cancer and a focus on cancer prevention and early diagnosis. This will ultimately be the key to improving the diagnosis and treatment of esophageal cancer.

At present, genetic studies on esophageal cancer mainly focus on the detection of early oncogenes and exploring their oncogenic mechanisms. As research on molecular biology continues to evolve, our understanding of the occurrence and development of malignant tumors and the phenomenon of life has been profoundly altered. In the future, with more in-depth research on the molecular biology of tumors, we can gain a better understanding of the pathogenesis of esophageal cancer and explore more effective treatment methods.

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